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RECENT DEVELOPMENTS IN SERUM SENSITIVITY TESTING.[1]

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ANTISERA of animal origin have been in medical use for nearly seventy years. Ever since the introduction in 1891 of the first antiserum, diphtheria antitoxin, allergic reactions have been reported. Reactions of this nature continue to be a constant source of worry to those who prepare, administer or receive animal serum products. Present-day methods of preparing a refined and concentrated antiserum have reduced the incidence of serum sickness from more than 40% to less than 5%, but according to Parish (1958) the incidence of the acute anaphylactic type of reaction has not been appreciably affected by modern processing. Nevertheless, this type of reaction is of comparatively rare occurrence.

Various screening tests have been devised to detect serum sensitivity, in an endeavour to avoid the giving of a large dose of serum to a hypersensitive patient, and thus to avert a possible catastrophe. These tests may be applied to all serum products, but are of particular importance with respect to tetanus antitoxin, which is used in large quantities and which, perhaps, is not being administered with the discrimination that is warranted by its sensitizing properties.

In this account some experiences with the intradermal method of testing for sensitivity will be dealt with, and the results presented of a clinical trial, initiated in Melbourne and now in operation throughout Australia, of a modification of the subcutaneous trial dose method of Laurent and Parish (1957).

Types of Screening Tests.

There are two schools of thought on the type of screening test which should be employed to detect sensitivity to horse serum. The first of these favours skin tests to detect local hypersensitivity, and bases its choice on the assumption that skin sensitivity and general sensitivity run parallel. This group of tests comprises the scratch, the prick, the intradermal and the conjunctival. The second school recommends the parenteral introduction of a small amount of antigen, and bases its recommendation on the assumption that, if general sensitivity is present, then the patient will react in a general but mild way.

The prick test, which originated in England, has gained few adherents in this country. The conjunctival test, although used extensively in America in conjunction with the intradermal test, has never attained any popularity here. Most adults and nearly all children object strongly

[1] Read at a meeting of the Section for the Study of Allergic Diseases of the Victorian Branch of the British Medical Association on August 6, 1959.

to this test, which, moreover, is not entirely free from risk, as serious inflammatory reactions have been reported from its use. Furthermore, both "false positive" and "false negative" results have been obtained with it. It is hard to understand why the scratch test has not been more widely used for testing for serum sensitivity. There is surely enough evidence to label horse serum a highly potent antigen, yet most authorities advocate a preliminary intradermal test, admittedly with a dilution of serum. These same authorities, moreover, stress the need always to perform a preliminary scratch test before proceeding to intradermal testing with allergens such as animal danders, foods, dusts and, more recently, penicillin. It would be expected that, if the exquisitely sensitive patient had skin-sensitizing antibodies, a scratch test would detect them. Dr. S. Brand demonstrated this in two cases of anaphylaxis which he described at the 1958 meeting of the Australian Society of Allergists (B.M.A.), and Dr. P. Ward Farmer has had similar experiences.

The Intradermal Test.

With respect to the intradermal test, it has been the standard practice for many years in many countries to carry out a preliminary intradermal skin test for the purpose of detecting sensitivity to horse serum. However, there appears to be no universal agreement upon the quantity and dilution of serum to be used. Three years ago a subcommittee of the Section for the Study of Allergic Diseases of the Victorian Branch of the British Medical Association (1957) proposed a sound procedure for the administration of horse serum by injection. It was recommended that to all patients requiring tetanus antitoxin an intradermal test dose of 0·02 ml. of a 1 in 10 dilution should be given. If a positive skin reaction occurred, accompanied by constitutional symptoms, no further antitoxin should be given until the merits of the case had been evaluated. If, on the other hand, a positive skin reaction occurred, but without a general reaction, it was recommended that a further test dose with undiluted serum be given subcutaneously.

Practitioners, by and large, have not adopted these recommendations. Some do not carry out any screening test at all, whilst others use undiluted serum with or without a control. As for the reasons for this failure to reach agreement on what should be a straightforward procedure, in the first place, it would appear that there exists a great deal of uncertainty arising from the conflicting opinions on the use of tetanus antitoxin as a prophylactic agent. In the second place, these opinions are often coloured by the legal aspects. Tetanus is not a very common disease, but it has a high mortality rate. In nearly half the fatal cases the wound of origin cannot be found at all or is so trivial that a physician is not consulted. As Christensen (1957) of the Mayo Clinic has pointed out, when tetanus has occurred after trivial wounds, patients with such wounds have usually, if not always, been unattended by a physician during the early phase. He therefore considers that, if the wound is superficial and can be satisfactorily cleansed, the administration of antitoxin can be omitted. Despite this rational concept many practitioners feel obliged, for medico-legal considerations, to administer antitoxin to every patient who presents himself with a break in the skin. The fact that they may be sensitizing their patients to horse serum appears to them to be of secondary importance. Other practitioners are more discriminating, assessing each case according to the nature and duration of the wound. Finally, serious doubts have been cast on the reliability of the intradermal test itself.

The Commonwealth Serum Laboratories have been concerned for a long time at reports of unduly high percentages of positive reactions in patients on intradermal testing with a 1 in 10 dilution of tetanus antitoxin. One hospital in New South Wales has reported that two out of every three patients tested reacted positively, and two Melbourne public hospitals have made similar observations. As the policy of these hospitals was to "desensitize" every positive reactor, the valuable time of nurses and precious casualty space were being occupied in carrying out a procedure of doubtful efficacy. Frequently two or three patients would be undergoing "desensitization" at the same time, and, as one sister somewhat ruefully said, "There is always someone being desensitized in my casualty department".

At the Alfred Hospital the sister in charge of the casualty department thought that the abnormal number of positive skin reactions might be related to the "Zephiran" solution in which the syringes were kept. It was, therefore, decided to investigate these reports, with a view to discovering why so many non-specific reactions were being obtained and to establishing whether there was an association between skin reactions and possible syringe contaminants. The routine procedure at the hospital was followed. Tuberculin syringes were soaked in various "Zephiran" solutions and rinsed several times in sterile running water, and then 0·1 ml. of a 1 in 10 dilution of tetanus antitoxin was injected intradermally, tricresol-saline being used as the control. The result was read at the end of thirty minutes. At that time casualties were scarce, and so volunteers were obtained from the medical, nursing and clerical staffs. This trial came to an abrupt end when a staff nurse unexpectedly developed a severe reaction which necessitated her admission to the sick nurses' ward. Because of its numerous interesting features, a detailed description of this particular case is given in what follows.

CASE I.—A woman, aged 21 years, had never to her knowledge previously been given horse serum, nor had she any personal or family history of allergy. Two tuberculin syringes which had been soaking in a 1 in 100 solution of "Zephiran" in spirit were used in this case. Each was rinsed several times in sterile running water. The first was used to draw up 0·1 ml. of tetanus antitoxin (diluted 1 in 10), whilst the second was used to draw up an equal volume of tricresol-saline. The skin was swabbed with ether, and the injections were introduced intradermally on the volar aspect of the forearm, the control being proximal, situated about 2 in. below the elbow flexure. There was an immediate local reaction at both inoculation sites—namely, a weal with a surrounding flare, which extended rapidly. At the end of 20 minutes at the control site there was a weal one inch in diameter with pseudopodia, whilst at the antitoxin site there was a larger weal 1·5 in. in diameter with even larger pseudopodia. By this time the entire volar surface of the forearm was erythematous. The flare surrounding the control had spread above the elbow for several inches up the arm. Thirty-five minutes after the injections she felt agitated and hot in the face and complained of itchiness around the eyes, and there was appreciable periorbital œdema. The injection sites had become intensely itchy, and numerous small urticarial weals had appeared. The patient's condition improved on intramuscular injection of adrenaline and "Piriton", but she felt very shaky and complained of a headache. She was transferred to the ward for observation. Two hours later she was much improved, and the control site reaction had subsided, but at the antitoxin site there was still a large weal with erythema, which persisted for a further four hours. Nine hours after the original inoculations generalized urticaria developed, the antitoxin site flared up again and became more irritable. She was given 2 ml. of "Antistin" without any improvement, and relief was obtained only after two adrenaline injections, each of 8 min. The next day she had completely recovered, and there were no further complications. Six weeks later, scratch tests were carried out on her in the allergy clinic with tricresol-saline, isotonic saline and "Zephiran" solution (1 in 1000). Surprisingly, all sites reacted, the possibility of dermatographia having been excluded. Tuberculin syringes had been used to draw up the solutions before applying them to the scratch. These syringes had previously been used for testing with antiserum, but they had been boiled in a sterilizer without having been thoroughly rinsed. Further scratch tests were now performed with autoclaved syringes from the Commonwealth Serum Laboratories. This time there was no reaction to isotonic saline or tricresol-saline, but within three minutes there appeared at the site of the tetanus antitoxin (diluted 1 in 10) a weal with pseudopodia and a flare several inches in diameter.

This subject was obviously so exquisitely sensitive that traces of antigen remaining in a syringe or a sterilizer were sufficient to provoke a local reaction. The reason for the positive reaction to the control at the time of the original trial was now apparent. It is interesting to speculate whether this nurse may not have been previously

sensitized by traces of antigen remaining in syringes used for the routine immunization of nurses. In this case a scratch test readily exposed her hypersensitivity, whilst an intradermal test provoked a severe response.

Sixty-two volunteers and three injured persons had already been tested intradermally when the mishap to the staff nurse occurred. Thirty-two (50%) stated that they had received tetanus antitoxin previously, and nine (14%) gave a history of a definite allergy. Fifty-one (78%) reacted in such a positive way that, had they presented themselves at the hospital with an injury, they would have been "desensitized". The three injured persons all reacted strongly to the intradermal test, and they were all subsequently given the full dose of antitoxin without the slightest untoward effect. Four persons reacted to the tricresol-saline control, three of them as strongly as to the serum. The numbers were too small to have any statistical significance with regard to the different "Zephiran" solutions, although there seemed to be little doubt that fewer positive reactions were obtained when autoclaved syringes known to be free from "Zephiran" were used.

There was one other interesting case which occurred during another series of tests. Again a staff nurse was involved.

CASE II.—This nurse, aged 22 years, had received tetanus antitoxin as a child, and, furthermore, she reacted strongly to house dust and pollens. The syringes used to carry out the intradermal tests in this series had been treated either by being boiled in water and then left to soak in "Zephiran" (1:100) solution, or by being thoroughly cleansed and autoclaved so as to free them from all contaminants. There was no reaction to tetanus antitoxin diluted 1 in 10 when a thoroughly cleansed and autoclaved syringe was used, but there was a weal about three-quarters of an inch in diameter, with a surrounding flare, at the site where a "Zephiran"-soaked syringe had been used to inject a similar amount of dilute tetanus antitoxin. The nurse then recalled that she developed a fine rash on her hands and forearms whenever she handled "Zephiran" in the wards. The response to a scratch test with 1 in 1000 "Zephiran" solution was negative, but that to an intradermal test with 1 in 10,000 "Zephiran" solution was positive.

Several reasons may be put forward to account for so many false positive reactions occurring after intradermal tests with horse serum. These are as follows:

1. The use of undiluted serum. Even a 1 in 10 dilution is apt to provoke a non-specific tissue response. Perhaps one should use a 1 in 50 or a 1 in 100 dilution. Ratner (1943), for example, advises a 1 in 1000 or a 1 in 10,000 dilution.

2. The injection of too large a volume. Many practitioners and hospitals have adopted 0·1 ml. as their routine intradermal dose. In fact, this is recommended by Gladstone (1958) in the second edition of Florey's "General Pathology". Most authorities agree that no more than 0·02 ml. should be injected intradermally when testing. This dose is not easy to measure accurately, and many practitioners do not appear to possess tuberculin syringes.

3. The presence of contaminants. On rare occasions, as with the two staff nurses mentioned above, contaminants may incite a reaction. Penicillin, "Zephiran" and tuberculin would appear to be the chief offenders.

4. Other reasons. Even when the above-mentioned precautions have been strictly observed, a certain number of non-sensitive individuals will react. The reaction may be due to the cresol preservative or to some other irritant contained in the serum, or it may be indicative of potential sensitivity. Occasionally a subject may react to all animal sera. Simon (1940) has demonstrated positive reactions to scratch tests with elephant, porpoise and other mammalian sera in dilutions of 1 in 10,000. Finally, Moynihan (1956), when using normal physiological saline or tap water as controls in a series of 200 patients, found that every one of these patients reacted with a flare and a weal at least 0·5 inch in diameter; 37·5% produced a control skin reaction of the same magnitude as the serum reaction. All the 200 were subsequently given the full dose of tetanus antiserum without any serious ill-effect.

"False negative" results with intradermal tetanus antitoxin tests have occurred also, but infrequently. Two children died in Queensland after tetanus antitoxin injections given when negative results had been obtained from intradermal tests, and three recent non-fatal cases may also be mentioned.

CASE III.—A boy, aged 14 years, with no history of previous administration of serum or of allergy, was given 0·1 ml. of undiluted tetanus antitoxin intradermally, without reaction. Thirty minutes after the full prophylactic dose had been administered he developed acute laryngeal œdema and severe urticaria.

CASE IV.—A child, aged five years, suffered a severe shock-like reaction several hours after a skin test had shown negative results. He was ill for two weeks.

CASE V.—A child, aged six years, gave no reaction to a skin test, but two hours after the full dose of antitoxin had been given he came out in a generalized rash, with œdema of the lips.

The number of practitioners who carry out skin tests with undiluted serum is remarkable. The dangers of such a procedure are obviously not fully appreciated, for of three deaths, one case of cardiac arrest and three very severe reactions which have recently occurred, the doctor in each case stated that the collapse followed a skin test with undiluted serum. In one case, that of a child, aged two-and-a-half years, the skin test was performed by a nurse. In two of the three fatal cases and in the case of the cardiac arrest the victims were asthmatics.

The Modified Subcutaneous Trial Dose Method.

Although a subcutaneous test to detect serum sensitivity had been mentioned from time to time by various authors, it was not until 1952 that this method of testing was given any publicity. In an article in the refresher course series for general practitioners published in the *British Medical Journal*, Laurent and Parish (1952) advocated the subcutaneous use of a small trial dose of serum. The object of this procedure was to observe the patient's general reaction to a small, slowly-absorbed dose of serum before the administration of a large dose. They asserted that the horse-serum-sensitive patient would react to a small dose and that such a reaction would be mild and easily treated. Furthermore, Laurent stated that he had used that method successfully for 25 years.

Laurent and Parish (1957) divided patients into three categories: (i) those with a history of allergy, particularly asthma or infantile eczema; for these patients they recommended a subcutaneous trial dose of 0·2 ml. of a 1 in 10 dilution of serum; (ii) those with no allergic history, but having previously had serum administered; for these patients they recommended 0·2 ml. of undiluted serum; (iii) the remainder, who had no history of allergy or previous serum administration, for these a full dose was advised, without the performance of any kind of preliminary test whatsoever.

This routine is open to criticism. Firstly, anaphylactic shock has occurred in patients with no history of allergy or previous serum administration. The consensus of opinion is that every person requiring an antiserum must be given some kind of preliminary test before receiving a full dose. Secondly, the trial doses recommended by Laurent and Parish may be dangerously high. This is exemplified by the following case:

CASE VI.—A young woman, aged 20 years, a sufferer from asthma and hay-fever, sustained a laceration of one of her fingers. She was given 1 min. of undiluted tetanus antitoxin subcutaneously. Three minutes later she complained of faintness and double vision, and marked bronchospasm was observed. She died within half an hour, despite the prompt administration of adrenaline. At the post-mortem examination, the lungs were found to be emphysematous and the bronchi filled with very tenacious mucus.

Apparently Laurent and Parish's recommendations were not generally acceptable to the medical profession, for Moynihan (1956) reported that in a survey of 37 English hospitals only six were found to have adopted their method. He further found that, of 8900 casualty patients treated at three hospitals, 1027 (11·5%) gave positive skin reac-

tions on intradermal testing, and that these patients were not given any further antitoxin.

Laurent and Parish (1958) stated:

> We have come to the conclusion, and many of our colleagues in various hospitals have too, that skin sensitivity and general sensitivity do not run parallel.

Laurent quoted his experience with more than 50 patients who had given strongly positive reactions to serum given intradermally in a dilution of 1 in 10, but who had given no general reaction whatsoever when a full dose of scarlatinal antitoxin was subsequently given intramuscularly.

Here in Australia, growing dissatisfaction with the intradermal method of testing led in May, 1957, to the Royal Melbourne Hospital's requesting that a 0·01 ml. dose of tetanus antitoxin be used as a subcutaneous trial dose. To meet this request the Commonwealth Serum Laboratories prepared a 1 in 50 dilution of serum, which was put up in single-dose vials containing 0·5 ml. It was intended that this modification of Laurent and Parish's dosage was to be used for all patients needing tetanus antitoxin, irrespective of their history. It was realized at the time that the dosage might later have to be further modified.

One important objection to this method is that the test is largely a subjective one. Some patients may be somewhat shocked on arrival, or may develop neurogenic shock when their wound is attended to, so that a mild general specific reaction to a trial dose may be overlooked or difficult to assess. In such cases it would be advisable to wait until all signs of shock had subsided before testing for sensitivity.

In order to obtain accurate information regarding the efficacy of this method, it was decided to observe closely a trial at one of the large hospitals—namely, the Alfred Hospital. Here it was fortunate that, thanks to the cooperation of the medical superintendent and the sister in charge of the casualty department, the following routine was adopted: any reaction to the trial or full dose was to be recorded by the resident medical officer, and the patient concerned was to be referred to the allergy clinic for further investigation. To date, 75,000 doses of tetanus antitoxin (diluted 1 in 50) have been issued to all States of Australia. At the Alfred Hospital over 4500 subcutaneous trial dose injections have been given since May, 1958; only nine patients have developed signs and symptoms of a general reaction. However, there have occurred six "false negative" reactions.

As for the signs and symptoms to look for after the subcutaneous trial dose of 0·5 ml. of a 1 in 50 dilution, we have so far very little first-hand information, as only the nine cases of a general reaction have occurred at the Alfred Hospital in the 4500 trials. These are briefly described below. In some instances it has not been possible to decide whether the shock syndrome was traumatic, vasovagal or anaphylactic in origin. It is well known that vasovagal shock proceeding to actual syncope may occasionally occur immediately after any injection. Some of the cases here described would appear to fall into this category. In all the nine cases the wounds had received prompt attention and were not considered to be tetanus-prone. Therefore, no further antitoxin was given, but primary immunization with toxoid was initiated.

CASE VII.—An asthmatic youth, aged 18 years, developed urticaria on the opposite arm ten minutes after the subcutaneous injection of the trial dose and this gradually spread all over his body. He had received tetanus antitoxin three years before.

CASE VIII.—A lad, aged 16 years, with a childhood history of asthma and a strong family history of allergy, complained of nausea 20 minutes after the trial dose and became pallid. There was no disturbance of blood pressure or pulse, and he recovered without any form of treatment. He had received tetanus antitoxin on three previous occasions.

CASE IX.—A New Australian patient, aged 35 years, five minutes after the trial dose became pale and sweated, and his pulse became feeble. He responded to adrenaline. He apparently had no history of allergy or of previous serum administration.

CASE X.—A youth aged 19 years, who suffered from perennial hay-fever, sustained a laceration of the scalp and concussion. Within four minutes after the trial dose his headache became worse, his tongue felt swollen, and he sweated, became nauseated and felt itchy all over. He was given adrenaline, with prompt relief. No rash developed. To his knowledge he had not previously received horse serum.

CASE XI.—A youth, aged 18 years, with no history of allergy, but to whom horse serum had been administered 12 years before, began to sweat and developed pallor and buzzing in the head 15 minutes after the trial dose. These symptoms were relieved by adrenaline.

CASE XII.—A milk carter, aged 26 years, a dust asthmatic, became pale and sweated 20 minutes after the trial dose while his hand was being sutured. He had received serum two years before. Scratch and intradermal tests with dilute horse serum gave negative results.

CASE XIII.—A boy, aged 12 years, with no history of allergy, had been given tetanus antitoxin twice previously. On the last occasion, 18 months before, he had felt nauseated and had developed a moderately severe local reaction. A few minutes after the trial dose he complained of feeling hot and sweaty. Five days later the trial dose was repeated; the injection appeared to be unduly painful, and within 15 minutes an itchy weal three-quarters of an inch in diameter appeared, with pseudopodia and surrounding flare. The boy seemed somewhat restless, but no other untoward effects were observed.

CASE XIV.—A woman, aged 38 years, who had recently emigrated from Israel, felt hot in the face and head and complained of a heaviness in her chest two minutes after the trial dose. Two hours afterwards her menses commenced, one week before the expected date. She stated that she occasionally noticed a heaviness in her chest. Five days later the test was repeated without the slightest reaction. There was no history of allergy or of previous serum administration.

CASE XV.—A schoolmaster, aged 45 years, who was in receipt of an Army pension for "deep anxiety state, dyspepsia and hypertension", ten minutes after the trial dose suddenly felt faint and had a convulsive seizure which lasted for about one and a half minutes. He was given adrenaline. Four hours later on his way home, he broke out into a sweat and vomited several times. He had never received horse serum before, but his son and his brother both suffered from bronchial asthma, although he himself had no allergic history.

To this list may be added one other case, which was recorded at another hospital.

CASE XVI.—A man, aged 22 years, had received tetanus antitoxin on no less than six previous occasions. He stated that he had suffered reactions after Salk and influenza injections. During the half-hour following the trial dose he developed periorbital œdema, pallor, headache and vomiting, and his systolic blood pressure fell to 40 mm. of mercury. He responded to adrenaline and antihistamines.

Of the six "false negative" reactions recorded at the Alfred Hospital and referred to earlier, two of the patients developed anaphylactic symptoms within five minutes of receiving 1500 units of tetanus antitoxin subcutaneously. Both of these were admitted to the hospital in a state of profound shock, but recovered after intensive therapy. Both patients had received tetanus antitoxin on several previous occasions without ill effects. Neither had an allergic history. In the other four cases the time of onset of the first symptom after the giving of the full dose of antitoxin was 10 minutes in two cases, 20 minutes in the third and 90 minutes in the last. These four patients all developed extensive urticaria. Profuse lachrymation was a feature in two of the cases. It is interesting to note that in one of these two cases a subsequent scratch test with a 1 in 10 dilution of tetanus antitoxin produced a large weal reaction. In two of the cases a large local reaction was observed at the trial dose injection site, but, as there were no systemic symptoms, the full dose of antitoxin was administered 30 minutes later with the following results.

CASE XVII.—A man, aged 21 years, within 10 minutes of receiving the full dose of serum, complained of faintness and general itchiness. At first his face was flushed, and in a few minutes urticarial weals appeared and there was appreciable swelling of his lips and periorbital tissues.

CASE XVIII.—An asthmatic child, aged 11 years, suffered a small abrasion to his scalp. Twenty minutes after the full dose of antitoxin he suddenly sneezed. Profuse rhinorrhœa and lachrymation ensued, whilst urticarial weals rapidly extended from the injection site to the rest of his body.

Another case of a "false negative" reaction is that recently encountered by a Victorian country practitioner, who supplied the following particulars.

CASE XIX.—A woman presented herself at the base hospital with a penetrating wound of three days' duration, complaining of stiffness of the jaw. A subcutaneous trial dose of dilute antitoxin was given; a local indurated area one and a quarter inches in diameter developed, but no general reaction occurred, although the patient was observed for one hour. She was then given 1500 units of antitoxin subcutaneously; within two minutes she collapsed with a severe anaphylactic reaction, and was resuscitated with difficulty.

This particular case is interesting, in that the doctor was concerned at the size of the local reaction to the trial injection. Similar observations have been occasionally made by others. At another hospital the only reactions observed in the course of 2500 trial doses were two local ones. In both these cases the full dose of antitoxin was later followed by a generalized rash.

The Royal Children's Hospital, Melbourne, recorded five local reactions, but no general reactions, in their first 1500 trial injections. Four children developed weals of significant size, and two of them subsequently returned with generalized urticaria. The fifth child developed urticaria on his back and shoulder, without apparently having any significant local reaction.

It can be seen, from a study of the foregoing case histories and hospital reports, that the subcutaneous trial dose has detected sensitivity in some cases, but has failed to do so in others. It is extremely doubtful whether a satisfactory screening dosage can be determined which will cover all sensitive persons. Individual sensitivity to horse serum varies widely, so that a trial dose which may be sufficient to detect general sensitivity in one person may fail to provoke a reaction in another, or may cause a dangerously severe reaction in the exquisitely sensitive individual.

The following two cases will serve to illustrate some of the pitfalls likely to be encountered.

CASE XX.—A boy, aged eight years, fell off a scooter and suffered multiple abrasions and lacerations. He was taken to a doctor's surgery by the father, who was unaware that his son had been actively immunized against tetanus one year before. As the boy was said to be an asthmatic, the doctor administered 2 min. of undiluted tetanus antitoxin, in his own words, "not strictly intradermally, probably partly subcutaneously". After 20 minutes there was a small weal and a flare. He then gave 4 min. of undiluted antitoxin subcutaneously. Fifteen minutes later the child was brought back to the surgery, acutely dyspnœic, cyanosed and shocked, with generalized giant urticaria. He was given adrenaline and oxygen and was rushed to hospital, where he improved after the administration of further adrenaline and antihistamines. Five hours after the initial skin test he again suddenly collapsed, coughed, vomited and rapidly became unconscious. His systolic blood pressure fell to 75 mm. of mercury, his pulse rate rose to 166 per minute and his respiration rate increased to 44 per minute. He eventually recovered after the administration of adrenaline, "Solu-Cortef" and oxygen.

CASE XXI.—A woman, aged 25 years, had received tetanus antitoxin 12 months before. The doctor stated that he gave her "an initial skin test of about 100 units subcutaneously rather than intradermally". Fifteen minutes later, as no reaction, either local or general, had occurred, the remainder of the 1500 unit ampoule was injected subcutaneously. Fifteen minutes after this injection the doctor was called by the patient's neighbour, who informed him that the patient was dead. The doctor found the patient pulseless and with an unrecordable blood pressure, but she was breathing imperceptibly. Adrenaline had no effect, but she subsequently recovered after several injections of "Methedrine". She was admitted to hospital, where she developed gross urticaria, which failed to respond to antihistamines, but which cleared dramatically after the administration of prednisolone.

Summary.

Any test designed to detect serum sensitivity must (i) be safe, (ii) be reliable, (iii) be easy to interpret, (iv) be simple to carry out and (v) give relatively little pain or discomfort.

The scratch test satisfies most of these requirements, but there remains a serious doubt of its reliability. The intradermal test *per se* fails in nearly every respect. It is not safe as at present practised, and even in skilled hands it may be difficult to perform. It is painful and may be distressing to children. Most patients object to a series of injections when all they have come for is "a needle to stop tetanus". It is certainly difficult to interpret, and there is plenty of evidence to justify its being classed as quite unreliable. The subcutaneous trial dose method is easy to perform and gives relatively little pain or discomfort. It is perhaps too early to assess its safety, reliability and interpretation; but to date all hospitals which have adopted this method have been very satisfied with it. The incidence of non-specific reactions has been reduced to a minimum, so that recourse to "desensitization" has become a rarity. There is no need for a control injection. Many of us have experienced the difficulty of carrying out two somewhat painful intradermal antitetanus injections in a frightened child, and then of having to complete his passive immunization half an hour later with a third injection. Admittedly, a few "false negative" results have occurred with this method; but no screening test has yet been devised which is perfectly and completely reliable.

Although such authorities as Laurent and Parish do not consider that skin sensitivity is an accurate indicator of general sensitivity, it would appear that an undue local reaction to a subcutaneous test may be of significance and should be regarded as a sign of sensitivity. Such a reaction apparently does not occur very often, but it is proposed to examine closely the next series of cases in order to get some idea of its incidence and significance.

Recommendations.

1. Encourage active immunization of the entire population. Obviously, the foregoing problems would not arise if the community was actively immunized against tetanus. The toxoids in current use are not likely to provoke an anaphylactic reaction, although they do occasionally produce an unpleasant local reaction. It is imperative that asthmatics and all persons attending allergy clinics be actively immunized without delay. It is striking how many of the persons who suffered serious serum reactions had received serum on previous occasions. These reactions would have been avoided had the patient been persuaded to undergo active immunization after an injury. It is strongly urged that whenever a patient has to be given antitoxin, active immunization be commenced at the same time.

2. Take a careful history in all cases. Beware of asthmatics. If it is absolutely essential that an allergic subject should receive serum, then its administration should be supervised by an allergist.

3. Advise practitioners to use the subcutaneous trial dose method with diluted serum. Under no circumstances should undiluted serum be used initially. Intradermal testing should be left to the trained allergist.

4. Observe the patient for at least half an hour after any injection of tetanus antitoxin, test or full dose. Always keep on hand adrenaline, an injectable corticosteroid and an injectable antihistaminic whenever serum injections are being given.

5. Keep the syringes used to administer antitoxin separate and do not use them for other injectable substances. Wash them thoroughly so that traces of antigen do not contaminate sterilizers. The policy of keeping syringes in antiseptic solutions, such as "Zephiran", should be discouraged.

6. Finally, remember that there is no real urgency in carrying out passive immunization with tetanus antitoxin. Screening tests for sensitivity may, therefore, be deferred

to a time that is more convenient both to doctor and to patient.

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A REPORT ON 500 CASES OF BLEEDING PEPTIC ULCER TREATED MEDICALLY WITH MINIMAL TRANSFUSION OF BLOOD.

By W. K. MANNING, M.R.A.C.P., AND K. O'CONNOR, M.B., B.S.,

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IN the issue of THE MEDICAL JOURNAL OF AUSTRALIA of November 12, 1955, a previous survey of this subject by one of us (W.K.M.) was published under the title "Observations upon 250 Cases of Bleeding Peptic Ulcer". The patients dealt with in this survey had been treated by a variety of methods, but after evaluation of the evidence two main conclusions in regard to treatment were drawn. The first conclusion was that surgical treatment as an emergency measure for bleeding should be discarded because of the absence of any rational basis of selection of patients, because the number of patients who could be saved by surgical treatment, and by surgical treatment alone, was probably relatively small, and because the mortality of emergency surgery in this condition is considerable. The second conclusion was that, in the medical treatment of bleeding peptic ulcer when the bleeding point was not subject to mechanical control, severe restriction of blood transfusion was a more effective method than the method of free transfusion as generally practised. The basis of objection to free transfusion of blood was that it tended to cause recurrence or continuance of bleeding, thus delaying recovery and increasing the likelihood of a fatal outcome. The practical observation that this was so was, of course, not new, and was merely the confirmation of a theoretical probability; the fact that hæmorrhage tends to be a self-limiting event, and therefore that transfusion tends to increase the likelihood of further hæmorrhage, can hardly be contested on theoretical grounds, and can be deduced readily from a description of the automatic protective mechanisms which operate after hæmorrhage, to be found in any textbook of physiology. It was held that the perfusion of donor blood through the vascular system and alimentary tract of these patients, as is so commonly practised, nullified the protective mechanisms referred to, and distressed the patients in various other ways, without achieving in many cases the only possible advantage to be gained—that is, a progressive elevation of the hæmoglobin level.

As a result of this survey, it was decided to treat a series of patients entirely according to the principles outlined above, and the series so treated is the subject of the present report.

Clinical Material.

During the period covered by this report it was arranged that all male patients with hæmorrhage from the upper part of the gastro-intestinal tract admitted to the Repatriation General Hospital, Concord, were to be treated in one ward. In this way all but a small minority of patients with bleeding peptic ulcer were concentrated in this ward, and the report deals with 500 consecutive patients with bleeding peptic ulcer admitted to the ward. An autopsy was performed in all fatal cases with two exceptions.

These patients were drawn from the male ex-servicemen of both World Wars living in the city of Sydney and its environs, together with a few serving soldiers—a group which could be accepted as a fairly representative cross-section of the Australian male populace aged over 35 years. This statement is supported by the age distribution statement below, which covers an age range from 18 to 87 years:

Under 40 years	114 patients.
40 to 49 years	146 patients.
50 to 59 years	115 patients.
Over 60 years	125 patients.

Site and Nature of Ulcer.

The conventional classification is set out below, though it is not considered possible to make such a classification with any degree of accuracy; this opinion is based on the wide disparities repeatedly noted between evidence obtained from barium meal reports (frequently serial) and clinical histories on the one hand, and laparotomy or autopsy findings on the other.

Chronic duodenal ulcer	285 patients.
Chronic gastric ulcer	54 patients.
Acute peptic ulceration	131 patients.
Anastomotic ulceration (following partial gastrectomy or gastroenterostomy)	30 patients.

Severity of Bleeding.

It is very difficult to find any reliable standard of comparison in regard to the severity of bleeding as between one series of reported cases and another. The obvious standard is the total amount of blood lost; but this figure is clearly affected by the method of treatment and is, moreover, often difficult to obtain. Recurrence of bleeding after admission to hospital is held by many to be an important indication of the potential severity of the illness; but it is difficult to see that the significance of the recurrence is dependent to any great extent on its relationship to the time of the patient's admission to hospital; in the present series one recurrence of bleeding either before or after admission was very common and did not seem to be of much value as an indication of the ultimate amount of blood lost. However, it seems logical to assume that the potential severity of bleeding from peptic ulcers (as a group) would not vary much from one large hospital series to another, as it is probable that the great majority of patients with the diagnosis of bleeding peptic ulcer are admitted to hospital in any civilized community irrespective of the severity of the bleeding, for obvious reasons.

For what they are worth, the following figures are quoted in relation to the present series. Of the 500 patients, 174 had hæmoglobin values of less than 8 grammes per 100 ml.; bleeding recurred after admission to hospital in 137 cases. We of course maintain that lower levels of hæmoglobin would have been reached and more recurrent bleeding experienced in this series had a policy of free transfusion been adhered to; this statement is strongly supported by figures quoted later in the report, indicating that in no case was it found necessary to use the large volumes of transfusion blood, to keep pace with recurrent blood loss, that are frequently used with a policy of free transfusion.

Natural History of Bleeding from Peptic Ulcer.

In the great majority of cases as observed in this series there was a fairly constant pattern of events. The first hæmorrhage was usually the major one, and in a considerable number of cases the episode ended there. In the remaining cases the bleeding recurred one or more times, usually during definite episodes lasting several hours and recognizable clinically by malaise, restlessness, abdominal distension or the signs of shock in varying degrees; in some cases the unmistakable odour of the flatus indicated that fresh blood was in the bowel; overt bleeding might occur early or late. As a rule, the interval between hæmorrhages was 12 hours or more, usually sufficiently long for a fairly accurate assessment of the degree of blood loss to be made by estimation of the hæmoglobin value; the amount of the blood loss in successive hæmorrhages tended to be smaller, and in most cases bleeding ceased altogether before dangerous levels had been reached.

In a very few cases the blood loss becomes continuous and severe; this may occur *ab initio*, or may supervene at any time in the course of the illness, and will usually cause death to ensue rapidly in spite of any treatment that may be attempted.

Plan of Treatment.

The treatment of bleeding was entirely medical in all cases and was in our hands.

Nursing Staff.

As was stated before, patients were concentrated in one ward with a relatively permanent staff specially trained in their observation and care.

Sedation.

Patients were nursed flat in bed on one pillow, and sedation was begun immediately with 6 grains of "Gardenal" given by intramuscular injection and continued with "Carbrital". Sedation was designed to keep the patient more or less continuously asleep for 24 to 48 hours or longer depending upon the turn of events; the amount of "Carbrital" necessary for this purpose varied a good deal, but on the average a dosage of about 1·5 grains every three hours throughout the 24 hours was used.

Feeding and Hydration.

Feeding and hydration were begun immediately, and continued with half-hourly feeds of milk, egg-flip or water given by the nurse. An oral intake of 60 to 100 oz. of fluid in 24 hours was aimed at; the regular feeding was not continued throughout the night unless the patient was severely dehydrated. Usually within 24 hours of the cessation of bleeding the patient demanded food, and normal feeding was then resumed. The urinary output on this regime was 20 to 30 oz. in the first 24 hours in the average case, rising to above normal levels on the second day. It was found advisable to rouse the patient every few hours to pass urine whilst under sedation; a full bladder was a common cause of restlessness. A fluid-balance chart was kept, and also a stool chart recording the character and amount of all stools.

Hæmoglobin Value.

The hæmoglobin value was estimated daily until bleeding had ceased.

Bowel Function.

Constipation was the rule after the cessation of bleeding and frequently caused discomfort and recurrence of abdominal pain about the fourth day, when relief was usually given by the administration of an enema.

Ambulation.

About the sixth or seventh day after the cessation of bleeding, patients were usually taken to the bathroom in a wheel-chair, and if no syncopal symptoms ensued they were then allowed to walk to the shower and toilet and to progress to full activity over the next three to four days, irrespective of hæmoglobin levels.

Transfusion.

Transfusion was withheld entirely whenever possible, and in all cases as long as possible; when considered necessary, it was given in the smallest effective amount. Transfusion was seldom considered if the hæmoglobin value was known to be 4 grammes per 100 ml. or more. Only 13 patients in this series received blood transfusion as an emergency measure, and the average amount transfused was about 1200 ml.; the largest amount transfused was 3500 ml., which was given to a patient who had had recurrent bleeding over a period of several weeks and whose lowest hæmoglobin value recorded was 2·9 grammes per 100 ml. Ten more patients were given transfusions some days after bleeding had ceased, to prevent the possible adverse effect of prolonged anæmia on complicating diseases known or suspected because the patients were not "picking up" in the usual fashion. In this connexion it is, of course, quite impossible to say when the likelihood of recurrent bleeding has passed; but it becomes increasingly unlikely after four or five days' quiescence. Free transfusion of packed cells was never withheld if, after a week's freedom from bleeding, any unsatisfactory clinical features were present which might be relieved by transfusion.

The indications accepted for emergency transfusion were in general terms as follows: (i) Recurrent bleeding which could be calculated as likely to reduce the hæmoglobin value below 3 or 4 grammes per 100 ml. (ii) Signs of shock persisting without relief much longer than an hour or so after apparent cessation of a bleeding episode in a patient resting in bed. Such persistence seldom occurs when the residual hæmoglobin value after the episode is above 3 grammes per 100 ml. No significance was attached to signs of shock occurring during or shortly after a hæmorrhage, as these signs are usually caused by the rate of blood loss and other factors, and often occur in cases in which the total volume of blood lost has been relatively small. (iii) Any signs of cerebral anoxia, such as marked restlessness, deterioration of mental acuity or disturbance of respiratory function in a patient lying in bed.

It goes without saying that wide experience in the continuous observation of these patients is of great assistance in deciding when transfusion is obligatory in a given case and how much blood should be given. However, as was previously stated, it was found necessary in this series to transfuse only 13 patients as an urgent measure, and the experience indicated that with patients who had been active and otherwise apparently in reasonable health, apart from peptic ulceration, recovery could confidently be anticipated without any transfusion in all but the odd case.

Blood grouping and cross-typing were not done as a routine, but only when low hæmoglobin values had been reached or some complicating disorder had been noted; hæmoglobin estimations were made daily (or sometimes more frequently) during the acute phase of the illness.

No blood-pressure or pulse charts were kept; but in all "active" cases the nursing and medical staff maintained close observation, and particular stress was laid on the accurate recording of all stools.

Results of Treatment.

Mortality.

In many reports on the treatment of bleeding peptic ulcer, the statement of mortality is made as a simple figure (often to a decimal point) without any qualification or explanation of the standards used in the assessment of the figure. The implication here is that no difficulty or possibility of serious error exists and that the figure is an absolute one.

We, on the other hand, consider that the mortality figure has significance only relative to the standards by which it is assessed, and that unless complete clinical and autopsy information is evaluated by an experienced clinician before a death is attributed to bleeding peptic

ulcer, then the resulting statistics are not likely to be of much value.

The possibility that death has been due to bleeding peptic ulcer must be considered in every case in which gastro-intestinal bleeding has occurred during the terminal illness; but often this possibility alone is considered, to the exclusion of more important and perhaps less obvious causes. Cases in which bleeding has been due to lesions other than peptic ulcer must first be excluded, and this can be done with certainty only by a post-mortem examination. After exclusion of this group there remains the group in which bleeding from peptic ulcer has occurred during the terminal illness. A careful survey of this group of cases over a period of 12 years at the Repatriation General Hospital, Concord, has disclosed that the proportional responsibility of bleeding peptic ulcer for these deaths has varied from 100% in some cases to practically nil in others.

An example in the latter category was the case of a man, aged 66 years, who was admitted to hospital after a hæmatemesis. His hæmoglobin value was 10 grammes per 100 ml. and his condition was excellent. Two days later he developed a severe myocardial infarction confirmed by electrocardiography, and two pints of blood were given by transfusion; he died shortly afterwards and an autopsy confirmed the presence of thrombosis of a coronary artery and a small duodenal ulcer, but showed no evidence of recurrent bleeding.

It is necessary therefore in each case to decide whether bleeding peptic ulcer was a primary or a secondary cause of death, or whether it was merely incidental and made no significant contribution to the death. Death from bleeding ulcer occurs in the otherwise normal patient only whilst blood loss is actually proceeding; if he survives the phase of active bleeding by more than an hour or so, he will recover. Therefore, if the patient who has had bleeding from an ulcer dies without there being evidence of terminal bleeding (that is, within a few hours of death), either overt or by the finding of fresh blood in the stomach or small bowel at autopsy, then it may be concluded that bleeding has not been the primary cause of death, but at most a secondary cause through the effect of anæmia (anoxia) on some other serious disease process which will always be found in these circumstances.

The assessment of the relative importance of anæmia as a secondary cause of death in such cases depends on the one hand upon the hæmoglobin value at death, and on the other hand upon the gravity of the primary disease. A fairly extensive experience with severe diseases of the heart, lungs and other organs at low hæmoglobin levels in this series of cases indicates that anæmic states above the hæmoglobin value of 4 grammes per 100 ml. seldom embarrass a patient in bed to any extent unless the primary disease is already at an advanced stage with a poor prognosis.

The survey of deaths at the Repatriation General Hospital, Concord, referred to above, has also indicated that a considerable proportion of fatal hæmorrhages occur in peptic ulcers (usually large gastric ulcers) that have developed apparently for the first time in patients who have become enfeebled by senility, or who have entered the near-terminal, often bed-ridden, stages of some chronic illness such as emphysema, heart disease, malignant disease, tuberculosis, cerebral vascular disease, chronic nephritis and so on; clinical records of these cases extending back over 20 to 40 years often contain no evidence of previous peptic ulceration.

To include in mortality figures for bleeding peptic ulcer cases in which bleeding was only incidental to death, and cases in which death from some other disease was already shortly inevitable—to include such cases, especially when no qualification is made, serves only to confuse discussion of the subject, and greatly reduces the value of the mortality figure as a yardstick for the evaluation of various methods of treatment in the really important group of cases in which bleeding ulcer is the chief disability.

In the assessment of mortality in relation to the present series, all patients who died with a history of gastro-intestinal bleeding were subjected to autopsy, with two exceptions. In most cases medical records extending back many years were available, and hæmoglobin values over the period of the illness up to the time of death were known; it was therefore possible to make a fairly accurate assessment of the cause of death. All cases in which bleeding was due to a lesion other than peptic ulcer were excluded, and four patients who had had bleeding from a peptic ulcer during their final illness were excluded on the grounds that the bleeding was not terminal or severe, and was clearly a minor factor in death due to some other well-established and adequate cause.

In two other fatal cases in which it was very doubtful that bleeding had been the main factor, death was counted as having resulted from bleeding ulcer.

One of these patients showed unaccountable distress with hæmoglobin values of 9 to 10 grammes per 100 ml. over a period, and died without any further significant overt bleeding and after transfusion; unfortunately permission for autopsy could not be obtained.

In the final analysis of the 500 consecutive cases of bleeding peptic ulcer in this series, a total of six patients were found to have died from this cause. Of only one of these six patients could it be said that he was otherwise in good health and free of any other serious disability.

Morbidity.

A good deal has been said and written about the dangers of allowing anæmia to persist after bleeding from peptic ulcer, because of the supposed harmful effects of "anoxia" on the vital functions of the body. To place such statements in proper perspective, it is necessary to recall that the body has a reserve potential for the supply of oxygen to its tissues (particularly its vital tissues) of at least 10 to 20 times the basic requirement at rest; it would not be expected, therefore, that a reduction in hæmoglobin value from, say, 16 to 4 grammes per 100 ml. would provide any serious problem of oxygen supply to vital organs in an otherwise healthy subject at rest.

In patients whose vital organs are affected by disease (particularly vascular disease), it is obvious that embarrassment of function will occur at higher hæmoglobin values. However, as has already been stated, in this series of cases it was found that embarrassment of function seldom occurred at values above 4 grammes per 100 ml. in patients who had chronic disease of the heart, lungs or kidneys, unless that disease was already in a very advanced stage—so much so as to have made the patient an invalid before the blood loss occurred.

As an example may be quoted the case case of a man, aged 60 years, known to have hypertension, to have suffered from coronary stenosis with left bundle branch block for three years, and to have quite severe peripheral vascular disease; he suffered no distress at a hæmoglobin level of 4 to 5 grammes per 100 ml., which rapidly rose to normal levels.

Another case in point is that of a man, aged 60 years, who had severe extensive bilateral bronchiectasis with widespread pulmonary fibrosis visible in the X-ray film; he was quite undistressed with a temperature of 102° F. and a hæmoglobin value of 2·8 grammes per 100 ml. shortly after recurrent gastro-intestinal bleeding.

In cases in which very advanced disease of vital organs, especially of the heart, was present, records at this hospital over many years show that the effect of sudden blood loss was often very rapid and severe. Death sometimes ensued within an hour or so when blood loss had not been severe, and autopsy in these cases has frequently disclosed extensive generalized pulmonary œdema, presumably as the result of left ventricular failure. The occurrence of pulmonary œdema has been very frequent, and has been noted both in cases in which no transfusion has been given and in cases in which there has been time for transfusion to be given. It seems likely, therefore, that blood transfusion in these cases may do only harm, unless it can be given immediately after the blood loss and before pulmonary œdema has developed; this is seldom possible.

The actual recorded morbidity in this series during the treatment period (apart from preexisting diseases already

known) was very low. Headache for a few days occurred in a few patients with low hæmoglobin levels. One man, aged 49 years, developed optic neuritis in one eye with an altitudinal visual field defect at a hæmoglobin value of 5 grammes per 100 ml. Three patients, aged respectively 67, 63 and 55 years, developed hemiplegia (presumably from thrombosis of cerebral vessels) at hæmoglobin values ranging from 8 to 11 grammes per 100 ml. The tendency to thrombosis would, if anything, be lessened by anæmia; but in the absence of definite evidence as to whether or not vascular thrombosis was present, there might be some slender ground for implicating anæmia with vascular stenosis as a causative factor. However, if there was such a relationship, it might have been expected to be more evident in the numerous patients in the older age groups with very much lower hæmoglobin levels. In any case, the small number of cases involved is probably no more than might be expected statistically amongst such a large group of older patients having treatment in bed.

Convalescence.

Most of the patients were ambulant and feeling well by the second week after the cessation of bleeding, and the hæmoglobin values had usually returned to normal or near normal levels within one month. It was considered desirable in most cases to retain the patient in hospital for three to four weeks in any case, in the hope of ensuring optimum healing of the ulcer.

Follow-up barium-meal X-ray examinations were made in many cases, but there was no evidence, either radiological or clinical, that any significant slowing of the rate of healing was caused by the anæmia usually present during the healing period.

Discussion.

Under this heading opportunity is taken to make some additional observations on the subject of bleeding peptic ulcer which arise out of the experience gained with this series of cases, and which seem to us to be worthy of emphasis.

Diagnosis.

It is quite clear that even in well-informed medical circles the diagnosis of bleeding peptic ulcer is frequently missed, and this observation does not by any means apply only to mild cases. The main reason for this failure is that melæna often occurs without hæmatemesis, and when it does, it is likely to be completely unrecognized by the patient or be regarded as "an attack of diarrhœa". If the patient consults a doctor, he may give a history of ulcer dyspepsia; but this is quite frequently absent and his symptoms may be simply those of anæmia. Even at this juncture it is remarkable how often the obvious pallor of severe anæmia will be overlooked; a patient seen by us with a hæmoglobin value of 6 grammes per 100 ml. had been thoroughly examined by a doctor with a higher degree in medicine, who had made a provisional diagnosis of "acute labyrinthitis".

Even when anæmia has been recognized in such cases, it is notable that some other diagnosis will almost always be preferred to that of bleeding ulcer—very often cancer of some sort. In our experience, anæmia in a male who is otherwise apparently reasonably healthy is due to unrecognized bleeding from a peptic ulcer in nine cases out of ten, and this probability is not materially altered by negative barium-meal X-ray findings or by the absence of a "typical" ulcer history. A "typical" ulcer history in cases of proven ulcer is forthcoming in only a minority of cases, and the serious limitations of radiology as a diagnostic aid have been mentioned earlier; a negative barium-meal X-ray finding should never be given too much weight in the assessment of a case. It is also probable that the importance of salicylates and "Butazolidin" as primary causes of gastro-intestinal hæmorrhage has been considerably overestimated.

Post-Hæmorrhagic Shock.

The clinical syndrome necessary for a diagnosis of "shock" is well enough known; but it is surprising how often in this context tachycardia alone is accepted as evidence of shock when it is, of course, only a sign of anæmia.

It is difficult to understand why so much emphasis is so often placed upon post-hæmorrhagic shock as a guide to prognosis and treatment in bleeding peptic ulcer; it is difficult to understand, because post-hæmorrhagic shock is dependent primarily upon the rate of blood loss and upon other factors such as nausea, dehydration, fear and exposure, and none of these factors have much bearing on prognosis, given reasonable treatment. If the rate of blood loss is rapid, shock may occur with relatively small losses, whereas if the rate of loss is slow enough to permit of replacement of fluid from the tissues, very serious depletion of hæmoglobin may occur without shock. Although theoretically death can occur with the loss of only one-third of the blood volume if the loss is rapid enough, in practice this has not been observed to happen in bleeding peptic ulcer, and death has always been related to the total quantity lost (that is, exsanguination) rather than to the rate of loss.

At residual hæmoglobin values over, say, 3 grammes per 100 ml. in the otherwise normal individual in bed, post-hæmorrhagic shock is a temporary event lasting only a few hours provided that sufficient tissue fluid is available to restore blood volume, and is not necessarily of any prognostic significance.

It is suggested, therefore, that signs of shock occurring in a patient with bleeding peptic ulcer should be regarded with much less alarm than is usually the case unless those signs are unduly severe or prolonged, and that more weight should be given to the total amount of blood lost as estimated clinically and by frequent hæmoglobin estimations.

Recurrent Invalidity from Bleeding Peptic Ulcer.

A well-defined group of patients were noted in this series who suffered over a period of years from recurrent gastro-intestinal hæmorrhage, often severe in nature, but who were otherwise in excellent health and remained free, or almost free, from ulcer pain, and in whom repeated investigations had usually revealed no definite evidence of peptic ulceration or any other cause for gastro-intestinal hæmorrhage. This group appeared to be suffering from recurrent acute or subacute peptic ulceration; but the notable feature was that this tendency to recurrent ulceration with bleeding seemed to be little affected by partial gastrectomy, and in this series a number of such patients were treated for recurrent bleeding after partial gastrectomy.

Summary.

Five hundred patients with bleeding peptic ulcer were treated under an exclusively medical programme, which relied mainly on the natural tendency to spontaneous arrest of hæmorrhage and reinforced this tendency with heavy sedation of the patient and appropriate supportive measures. Transfusion of blood was used sparingly and only for the relief of anoxia, local or general.

A mortality rate of between 1% and 2% was achieved and only one fatality was due to peptic ulceration uncomplicated by some other significant disorder. Mortality was observed to be closely correlated, not with chronological age *per se*, but with the existence of chronic and serious coexisting disease of other organs, or with a generally feeble physical state associated with prolonged invalidism or senility. In this group of cases customary therapeutic procedures are often impracticable or ineffective, and blood loss, which may be quite moderate, frequently does no more than precipitate death already determined by other pathological conditions.

Acknowledgement.

Our thanks are due to the Chairman of the Repatriation Commission for permission to publish this article.

THE RISE AND DECLINE OF PINK DISEASE.

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THE recognition, description, and now the almost complet disappearance of pink disease present a number of interesting features. Swift, of Adelaide, is usually credited with the first full description of the disease, which he gave to the Australasian Medical Congress in Auckland in 1914 (Swift, 1914). However, it would appear that a number of earlier writers made reference to the condition. Professor Sir Edward Ford has drawn my attention to a report by Dr. Bancroft, of Brisbane, to the local Board of Health in 1881, that he "sees many children brought to death's door from their parents dosing them with a powerful powder of mercury . . .". Selter, of Solingen in the Ruhr (Wood and Wood, 1935), published a good description of the disease in 1903. Swift's description was apparently based on 14 cases in his practice in the preceding two years, although he had been shown an occasional child with this condition by Dr. Still in London some years earlier.

In 1920, A. J. Wood presented a paper to the Eleventh Australasian Medical Congress in Brisbane, basing his clinical description on the records of some 51 cases in his practice in the preceding six years or so (Wood, 1920). In 1935, A. J. Wood and his son Ian, in a report to the annual meeting of the British Medical Association in Melbourne, indicated that their series totalled 150, of which 60 had been added between 1920 and 1935 (Wood and Wood, 1935). The next major contribution to the Australian literature on this disease was made by Southby in 1949, when he was able to draw upon the records of 502 children diagnosed as having had this condition. This total was made up partly from his experiences in his private and hospital practices, and partly from the practices of some of his colleagues (Southby, 1949).

This brief review of the source material for the major Australian contribution suggests either a wider recognition or a mounting incidence from the first recognition through to the late 1940's. This would seem to parallel events in England and Wales. Logan (1949) has shown that the death rates from pink disease of children aged under five years rapidly mounted from 0·3 per million in 1923 to a peak of 31·4 per million in 1936. For a few years the numbers fluctuated and then they dropped to a lower plateau, which continued at around 17·0 per million until 1946. In 1947 there was a sharp rise to 29·0 per million. Logan suggested that the widening recognition of the disease was probably responsible for the steady rise in death rates to the plateau which commenced in the early 1940's. Since 1948 there has been a sharp decline to almost disappearance (see Figure I). This will be discussed later.

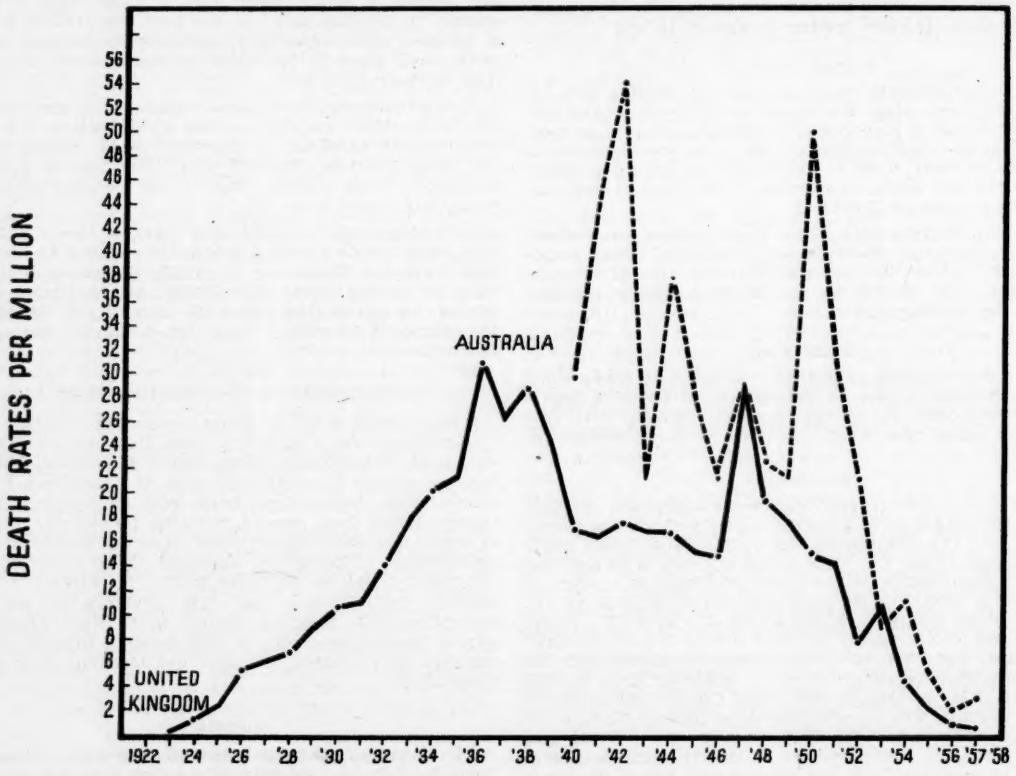

FIGURE I.
Death rates for pink disease in children aged under five years in the United Kingdom and Australia.

Control of a disease is dependent upon the definition of the ætiology. For many years the ætiology of pink disease has been the subject of much speculation and some experimentation. Earlier theories covered a wide range of possibilities, including an allergic response, endocrine dysfunction, poisoning by arsenic and ergot, an infective agent. Some of these, like the arsenic and ergot theories, were disposed of; but the difficulties of testing other hypotheses left some of them still possibilities when Fanconi and his co-workers (1947)

[1] Endowed by the Commonwealth Department of Health.

suggested that mercury poisoning and/or sensitivity was the main or perhaps the only ætiological factor. This hypothesis, which was supported by the work of Warkany and Hubbard a year or so later, offered for the first time a possible tangible objective for the control of pink disease — namely, the removal of mercury from teething powders and syrups, the commonest source for infants and young children, and perhaps the restricted use of mercurial ointments on young children. Action to this end occurred in England before it did in Australia. Colver (1956) points out that the warnings by prominent pædiatricians and public-health workers in the early 1950's (Gaisford, 1949; James, 1951) considerably reduced the number of prescriptions written by doctors, and ultimately led to the withdrawal by a principal manufacturer of mercury from teething powders. This was effective in December, 1953,[1] although some small manufacturers and pharmacists still appeared to be including the metal in locally dispensed powders (Dathan and Macaulay, 1955). It has apparently not been thought necessary to introduce legislation in England to control the use of mercury in teething powders. Colver (1956) has shown that between 1947 and 1955 there was a reduction of about 75% in the number of patients with pink disease treated at the Sheffield Children's Hospital and the City General Hospital.

The analysis of death rates in England and Wales commenced by Logan has been extended from subsequent annual reports by the Registrar-General, and the figures are incorporated in Figure I. It will be seen that, from a plateau of around 30 deaths per million (based on the population aged under five years) in the late 1940's, the rate has fallen to an insignificant point in 1957.

The sequence of events in Australia will now be reveiwed.

Legislation in Australia to Control the Use of Mercury in Teething Powders.

On August 20, 1953, the South Australian Government promulgated a regulation prohibiting the use of mercury in teething powders unless prescribed by a medical practitioner.

On June 15, 1954, the following regulation (75A) was gazetted in Queensland:

> No person, other than upon the written prescription of a medical practitioner, shall sell any teething powder, soothing powder, infant powder or similar preparation containing mercurous chloride for internal use by children under five years of age.

Similar regulations were gazetted in Tasmania on April 27, 1955, in New South Wales on August 10, 1956, and in Victoria on October 22, 1956. Although specific legislation on this matter has not been introduced in Western Australia, the Commissioner of Public Health has advised that the problem is adequately controlled by existing legislation (Henzell, 1957).

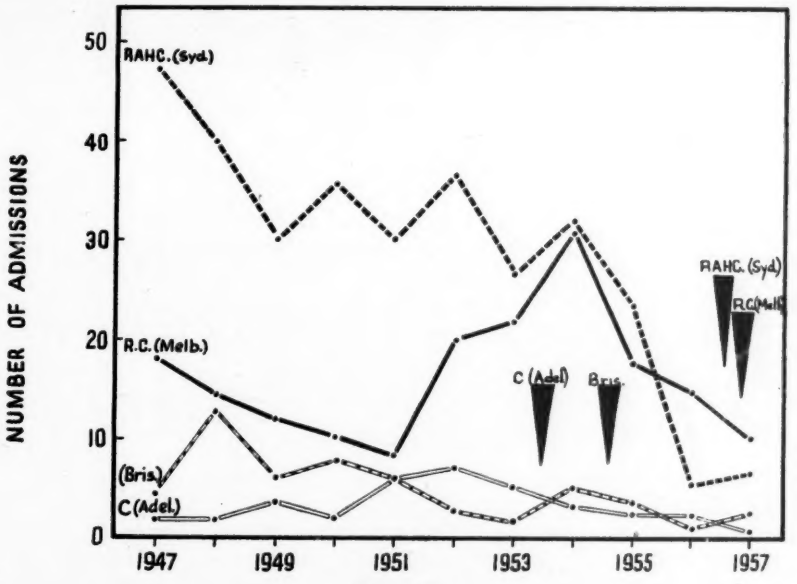

FIGURE II.

Numbers of children with pink disease admitted to the Royal Alexandra Hospital for Children, Sydney (RAHC, Syd.), the Royal Children's Hospital, Melbourne (R.C. Melb.), the Adelaide Children's Hospital, Incorporated (C. Adel.), and the children's ward of the Mater Misericordiæ Hospital, Brisbane (Bris.).

Almost complete Australia-wide legislation is due in no small measure to the efforts of the Australian Pædiatric Association, both as a corporate organization and through the personal efforts of individual members in each State. It is of interest to record that, although the regulation was promulgated in New South Wales on August 10, 1956, teething powders containing mercury were purchased from a large number of pharmacists as late as the first quarter of 1958. It is suggested that this was due to the lack of publicity given to the new regulation. The position has since been rectified. This point is stressed because of its relationship to trends in morbidity and mortality.

The Incidence of Pink Disease.

The exact incidence of this condition cannot be estimated accurately. It is not a notifiable disease, and minor forms are probably not recognized. A hospital tends to attract patients with specific diseases if special facilities are provided for their diagnosis and treatment. For a number of years a pink disease clinic was conducted at the Royal Alexandra Hospital for Children. In the middle 1950's special facilities existed at the Royal Children's Hospital, Melbourne. These services may have had some influence on the figures given for the numbers of children treated at the various hospitals. The numbers of children treated

[1] *Brit. med. J.*, 1953, 2: 1330.

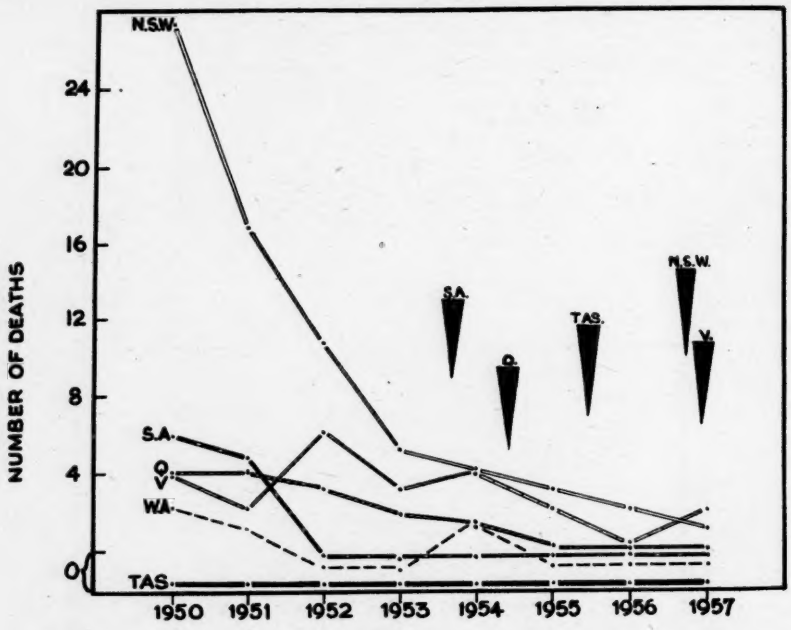

FIGURE III.

Numbers of deaths from pink disease in each of the Australian States. The arrows indicate the date of introduction of the legislation controlling the use of calomel in teething powders.

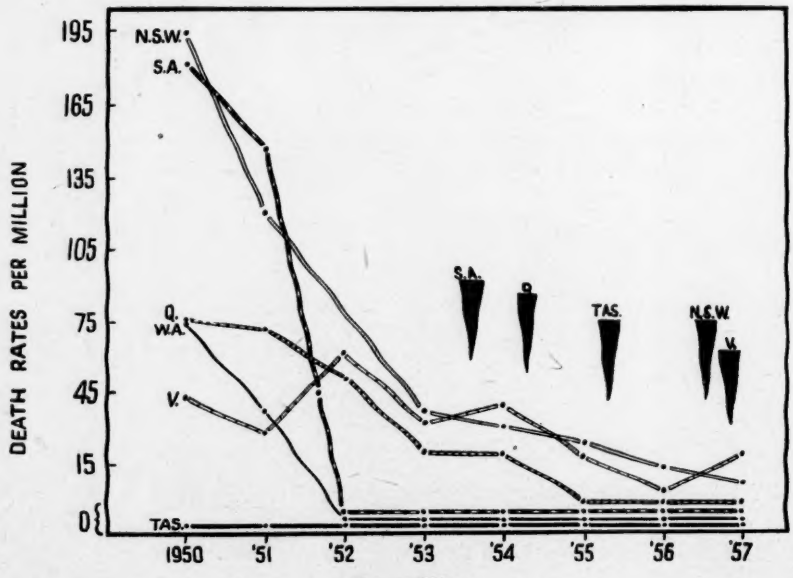

FIGURE IV.

Death rates from pink disease per million children aged under two years in the six Australian States.

at the Royal Alexandra Hospital for Children, Sydney, the Royal Children's Hospital, Melbourne, the Adelaide Children's Hospital (Incorporated), Adelaide, and the Mater Children's Hospital, Brisbane, over the eleven-year period 1947-1957, are shown in Figure II. The arrows on this chart indicate the approximate dates of introduction of legislation in each State to control the use of mercury.

Trends in Mortality.

The numbers of children who died with the diagnosis "pink disease" were first recorded in official Australian statistics in 1940. In 1948 the Sixth Revision of the International Classification of Diseases and Causes of Death was introduced, but it was not adopted for Australian official statistics until 1950. However, these

changes did not affect the recording. The trend in mortality in Australia is shown on Figure I, along with the trend in England and Wales. For comparison, the Australian rates are expressed in the same terms as those for England and Wales — namely, deaths per million children aged under five years. Since few deaths occur above the age of two years, a better rate would have been for children aged under two years.

A feature of the Australian data is the wide fluctuations from year to year, for which there does not appear to be any explanation. With the exception of the year 1950, the trend has been progressively downward, until the current rates are but a fraction of what they were in the 1940's. It is nevertheless disconcerting to note that, throughout the years for which both English and Australian figures are available, the Australian rates have been appreciably higher.

Some interesting facts emerged when the numbers of deaths and the death rates for the various States were compared. These figures are shown in Figures III and IV. It will be noted that initially high rates existed in New South Wales and South Australia, with almost insignificant figures for Tasmania. The differences between the States may well be a reflection of interest and enthusiasm in diagnosis. Attention is drawn to the arrows in Figures II and III, which indicate the approximate date when the legislation was introduced in each State to control the sale of teething powders containing mercury. The position of each of these arrows in relation to the shape of the curves in Figure IV is of particular interest.

Discussion.

Pink disease is fast disappearing, and will, no doubt, shortly join the long list of diseases of childhood which in the last two or three decades have become rarities, to be displayed at a clinical evening. The cause of the disappearance is not clear. The conclusions to be drawn from Figures II and IV do not support the implication that legislative control of the use of mercury in teething powders is the cause. The fall in both the numbers of children admitted to hospital and mortality rates had occurred before the legislation could have been effective. Analysis of teething powders showed that voluntary exclusion by manufacturers or pharmacists had not preceded the legislation. It is interesting to note that the trend of mortality in England is similar to that in Australia, and there the removal of mercury was on a voluntary basis.

It could be argued that over the past decade fewer teething powders were given to young children, the mothers responding to the educational efforts of baby health centre nurses and others. Unfortunately we have no evidence to test this suggestion, and we have been unable to obtain any figures for the sale of teething powders over the years. The apparent ineffectiveness of legislation is disappointing to those who worked for this action; but it is important to record these changes in a disease pattern now, lest at some time in the future an attempt is made to use the virtual disappearance of pink disease so soon after the introduction of legislation as an example of the effectiveness of this form of disease control.

Although the late Frank Barrett (Barrett, 1957) at one time strongly held, as a result of his extensive animal experimental work, that pink disease was due to mercury poisoning, and although several English writers have claimed that the disappearance of the condition in England is proof of the implication of mercury in the ætiology, the Australian statistical information certainly does not support this point. Neither does it deny the hypothesis. For the sake of the theory, it is unfortunate that the spectacular fall in death rates should have preceded the introduction of the legislation.

Summary.

1. A brief outline is given of the main reports published in Australia on pink disease.

2. It is pointed out that, in both the United Kingdom and Australia, death rates rose from a low level when the condition was first recorded to a peak in the late 1940's and now the disease has almost disappeared.

3. The number of hospital admissions for this condition in the four major children's hospitals in Australia has roughly paralleled the mortality rates.

4. The dates of the introduction of the legislation in five Australian States to control the dispensing of mercury in teething powders and syrups are recorded. It is pointed out that the sharp decline in both morbidity and mortality preceded the introduction of legislation.

5. Although calomel may be a main ætiological factor in pink disease, the demographical information neither substantiates nor denies this hypothesis.

Acknowledgements.

Sincere appreciation is expressed to Dr. V. Collins, Melbourne, Dr. E. Sims, Adelaide, and Dr. David Jackson, Brisbane, for arranging for the compilation of the figures on hospital admissions at their respective hospitals. Thanks are especially accorded to Dr. J. Fulton for making available the records of the Royal Alexandra Hospital for Children, Sydney, and to Miss P. Grave, of the Institute staff, who assisted in the compilation of the Sydney figures.

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SPECIFIC IMMUNITY AGAINST STAPHYLOCOCCUS INFECTION IN MICE NOT ASSOCIATED WITH *DEMONSTRABLE ANTIBODY* IN THE SERUM: INTERFERENCE EFFECT.

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TEN years ago Henle (1950) reviewed the literature concerning "interference" phenomena between animal viruses. He concluded, *inter alia*, that many of the recorded instances of interference are based on a close interaction between virus and host cell, the interfering virus (active or inactivated) blockading the cell.

Some years later, Evans and Perkins (*1954a*) reported the ability of pertussis vaccine to produce in mice specific immunity of a type which appeared to be independent of circulating antibodies. They later showed (Evans and Perkins, *1954b*) that pertussis vaccine in the form of either a killed bacterial suspension or a cell-free extract,

TABLE I.

Effect of "Living" Staphylococcus Vaccine on Experimental Staphylococcus Infection in Mice.[1]

Group.	Day Challenged After Final Dose of Vaccine.	Day of Death after Challenge.		Survivors at Seven Days.	
		Vaccinated Mice.	Unvaccinated Mice.	Vaccinated.	Unvaccinated.
1	14	1 1 1 1 1 2 2 2 2	1 1 1 1 1 1 1 1 6	1/10	0/10
2	21	1 1 1 2 5 7	1 1 1 1 1 1 1 1 1	4/10	0/10
3	28	1 1 1 2 2 3 4	1 1 1 1 1 1 1 3	3/10	1/10
4	35	1 1 1 1 1 3 6	1 1 1 1 1 1 1 1 3	3/10	0/10
5	41	1 1 1 1 3	1 1 1 1 1 1 1	5/10	2/9
6	48	1 2	1 1 1 1 1 1 2 3	8/10	1/9
7	55	1 2 3	1 1 1 1 2 2 3 7	7/10	2/10

[1] Mice were challenged intraperitoneally on the day shown in the second column after the final subcutaneous dose of vaccine. Experiments were terminated seven days after challenge with the homologous strain S1531.

was able to interfere with the development of fatal pertussis infection in the mouse.

Finally, Evans and Perkins (1955) showed that this early interference immunity following a single injection of pertussis vaccine was of a transient type, and that it was quite distinct from an immunity which developed later and was probably serological in nature.

We have been studying active immunization of mice against experimental staphylococcus infection, and have found a type of immunity which, in many ways, is similar to that described by Evans and Perkins against experimental *Hæmophilus pertussis* infections.

Materials and Methods.

Experimental Animals.

Albino mice of the strain maintained at the Commonwealth Serum Laboratories were used throughout. They weighed 20 to 22 grammes when immunization was commenced. Mice of only one sex — either male or female — were used in any one experiment.

Vaccines.

A "standard" or reference vaccine was prepared as follows, from a virulent strain of staphylococcus S1531, used in other studies (North, 1958, 1959). The overnight growth on veal infusion agar was washed off in normal saline, standardized by means of Brown's ("Wellcome") opacity tubes to contain 80 international opacity units and killed with formalin (1: 8000 formaldehyde) by standing for 45 hours at 37° C.

Part of a "standard" vaccine was immersed in boiling water for 30 minutes.

A *Staphylococcus albus* vaccine was prepared from a strain (S805) that was non-hæmolytic, did not produce coagulase and was non-pathogenic for mice. The procedure was the same as for preparation of "standard" vaccine, except that only 24 hours' incubation with formalin was required to kill all the cells.

Supernatants were prepared by spinning a bacterial vaccine at 28,000 G for 30 minutes and filtering through sintered glass.

Of the streptococcus vaccines, one was a stock C.S.L. polyvalent vaccine. A second vaccine was prepared from an overnight blood agar culture of Strain 270 by suspending it in saline and heating it with formalin as for "standard" staphylococcus vaccine, except that it was left standing for 24 hours at 37° C.

Administration of Vaccine.—All vaccines were injected subcutaneously in doses of 0·5 or 1 ml.

Determination of In Vivo Active Immunity.

Mice were challenged intraperitoneally with overnight veal infusion broth culture of a virulent strain, either S1531 or S1983. The volume injected varied between 0·5 and 0·6 ml., according to the size of the mice when challenged. Such doses usualy killed 70% to 100% of non-immunized mice. Hæmolysin was not detected in the supernatant, 1 ml. of which was harmless to mice when injected intravenously (North, 1959). Experiments were terminated seven days after challenge.

Determination of Serum Antibody Titres.

Mice were exsanguinated under ether, and the sera were pooled and tested as follows: (i) Antihæmolysin was tested for by Burnet's method (Burnet, 1931). (ii) Protective antibody was tested for in mice (North, 1959), the mice being challenged 24 hours after subcutaneous injection of serum.

Results.

Immunity Following Injection of Vaccine Containing Living Staphylococci.

When this work was started, there were few data or none on what might constitute a "good" or a "poor" staphylococcus vaccine. It was thought that, on general principles, a vaccine inactivated by the use of a minimum concentration of formaldehyde at 37° C. for the shortest possible time might be a good antigen.

In an early experiment, we used a vaccine which was insufficiently inactivated. As 100 mice had already been injected with the first of a course of two doses of this vaccine before its lack of complete sterility was found, we continued the experiment. Some suppuration and dermonecrosis developed at the site of injection, but the mice showed no signs of general ill-health.

Groups of immunized and unimmunized mice (Table I) were challenged at intervals from 14 to 55 days after

TABLE II.

Effect of Two Injections of "Standard" Vaccine on Experimental Staphylococcus Infection in Mice.[1]

Group.	Day Challenged after Final Dose of Vaccine.	Day of Death after Challenge.		Survivors at Seven Days.	
		Vaccinated Mice.	Unvaccinated Mice.	Vaccinated.	Unvaccinated.
1	7	1 1 1 1 1 1 1 1 1	1 1 1 1 1 1 1 2	0/10	0/9
2	13	1 1 1 1 1 1 1 1 2	1 1 1 1 1 1 1 1 1	0/10	0/10
3	20	1 1 1 1 1 1 1 2 2	1 1 1 1 1 1 1 1 1	0/10	0/10
4	27	1 1 1 1 1 1 1 1 1	1 1 1 1 1 1 1 6	0/10	1/10
5	34	1 1 1 1 1 2 7	1 1 1 1 1 7	3/10	3/10
6	41	1 1 1 1 1	1 1 1 1 2	5/10	5/10
7	48	1 1 1 1 1 7	1 1 1 1 1 1 1 1	4/10	2/10
8	55	1 1 1 1 1 1 2	1 1 1 1 1 1 1 2	3/10	1/10
9	55	1 1 1 1 1 1 2 2	1 1 1 1 1 1 1	2/10	3/10

[1] Mice were challenged intraperitoneally on the day shown in the second column after final subcutaneous dose of vaccine. Experiments were terminated seven days after challenge with the homologous strain S1531.

TABLE III.

Effect of Four Injections of "Standard" Vaccine on Experimental Staphylococcus Infection in Mice.[1]

Group.	Dose of Vaccine. (Millilitre.)	Day Challenged after Final Dose of Vaccine.	Day of Death after Challenge.		Survivors at Seven Days.	
			Vaccinated Mice.	Unvaccinated Mice.	Vaccinated.	Unvaccinated.
1	0·5	2	1 1 2	1 1 1 1 1	7/10	5/10
	1·0		1		9/10	
2	0·5	9	1 1 1 1 1 1 2 2 5 6	1 1 1 1 1 1 1 1 1 4	0/10	1/10
	1·0		1 1 1 1 1 1 1		3/10	
3	0·5	16	1 1 1 1 1 2	1 1 1 1 1 1 1 1 1 1	4/10	1/10
	1·0		1 1 1 1 1 1 1 1		2/10	
4	0·5	17	1 1 1 1 1 1 1 5	1 1 1 1 1 1	2/10	4/10
	1·0		1 1 1 1 1		5/10	
5, 6	0·5	37	1 1 1 1 1 1 1 1 1	1 1 1 1 1 1 1 1 1 2	4/20	11/20
			2 2 2 2 5 6 6			
	1·0		1 1 2 2 6		12/17	

[1] Mice were challenged intraperitoneally on the day shown in the third column after final subcutaneous dose of vaccine. Experiments were terminated seven days after challenge with the homologous strain S1531.

the vaccinated mice had received the second dose of "living" vaccine. At all time intervals tested, the vaccinated mice showed some degree of protection compared with the unvaccinated control group. However, as may be seen from Table I, the degree of protection was statistically significant only once—on the twenty-first day—until seven weeks or more after the last injection of vaccine.

Immunity Following Multiple Injections of "Killed" Standard Vaccine.

The results obtained with the "living" vaccine encouraged our belief that a "standard" vaccine would protect mice against subsequent lethal challenge if a suitable schedule of dosage was chosen.

Groups of mice were accordingly injected with varying sizes and number of doses of "standard" vaccine at intervals of seven days or less. They were then challenged at intervals after the last injection of vaccine, together with suitable control groups. However, it soon became clear, that, irrespective of the dosage schedule of vaccine used, the mice were protected poorly, if at all.

Table II shows the results of protection tests on mice given two doses of "standard" vaccine and challenged with the homologous strain at intervals ranging from seven to 55 days after the final dose of vaccine. It will be seen that little or no protection is evident after challenge at any time. Mice of Groups 8 and 9 were both challenged at 55 days to see if the larger number of animals would help to clarify the issue.

Table III shows the result of a representative experiment on mice, in which four doses consisting of either 0·5 or 1·0 ml. of "standard" vaccine were administered. Groups of immunized and unimmunized animals were challenged at intervals commencing, in this case, two days after the last injection of vaccine. The only clear evidence of protection is in the group of mice challenged two days after the last injection of vaccine. Of the groups challenged 37 days after the final immunizing dose, those that received the smaller doses (0·5 ml.) fared worse than the control group; those that received the larger doses (1·0 ml.) did somewhat better than the controls, but not significantly so.

Experiments Using a Single Dose of Vaccine or Other Immunizing Agent.

The experimental result shown in Table III was only one of a number which showed the same feature—namely, definite but transient protection a few days after the final dose of vaccine. The effect of a single dose of vaccine on subsequent protection was therefore investigated, and Table IV shows the protocol of a representative experiment, in which the mice were challenged with the homologous Strain S1531. It will be seen that no protection was demonstrated five hours after the injection of the vaccine, that there was maximum protection about two days later, and that protection had almost completely faded out after two weeks.

The results of an experiment using the "standard" vaccine prepared from S1531 but a heterologous strain for challenge (S1983) are shown in Table V. It is evident that the interference effect is just as marked as when the homologous strain is used for challenge.

Table VI shows the results of a representative experiment in which the interference effect of "standard" vaccine (Group I mice) was compared with that of a part of the same vaccine boiled for 30 minutes (Group II), and with that of a vaccine prepared from a non-pathogenic staphylococcus S805 (Group III mice). The fact that in this and in another experiment the *Staph. albus* vaccine was more effective was wholly unexpected. Further, it would appear that boiling a vaccine for half an hour (comparing Groups I, II and V) has relatively little effect on its efficacy as an "interfering" agent.

On the other hand, comparing Groups I, II and III with Groups IV and V, it would appear that the effect is a specific one, in that a streptococcus vaccine gave no protection whatever.

Table VII shows the protocol of one of two experiments with similar results, in which 1 ml. of filtered supernatant of a "standard" vaccine (Group I mice) proved to be an effective interfering agent. It also shows the results of another experiment, in which the protective effect of

TABLE IV.

Effect of Time Interval between Intraperitoneal Challenge and a Single Injection of Vaccine Prepared from Homologous Strain of Staphylococcus (S1531).[1]

Group.	Time between Vaccine and Challenge.	Day of Death after Challenge.	Survivors at Seven Days.
1	5 hours.	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	0/20
2	2 days.	1 1 1 1 1 1 1 1 1 1	8/18
3	7 days.	1 1 1 1 1 1 1 1 1 1 1 2	7/20
4	14 days.	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 2 3 4 4	1/20
5	No vaccine (controls).	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 4	1/20

[1] Mice were divided into five groups and vaccine was administered to Groups 1, 2, 3 and 4 at times shown in the second column before all five groups were challenged simultaneously. Experiment was terminated seven days later.

TABLE V.

"Interference" Effect with the Use of Heterologous Challenge Strain (S1983) of Staphylococcus against Mice Immunized with "Standard" Vaccine (S1531).[1]

Group.	Time between Vaccine and Challenge.	Day of Death after Challenge.	Survivors at Seven Days.
1	2 days.	1 1 2 2	16/20
2	7 days.	1 1 5	17/20
3	14 days.	1 1 1 1 1 1 1 1 1 1 1 1 2 2	5/20
4	No vaccine (controls).	1 1 1 1 1 1 1 1 1 1 1 1 2 2 5	5/20

[1] Eighty mice were divided into four groups and vaccine was administered to Groups 1, 2 and 3 on days shown in the second column before all four groups were simultaneously challenged intraperitoneally with heterologous strain (S1983). The experiment was terminated seven days later.

the filtered supernatant of a vaccine prepared from a non-pathogen (S805) (Group IV) is compared with that of streptococcus and "standard" *Staph. aureus* vaccines (Groups III and V). It will be noticed that there were fewer survivors amongst mice that received streptococcus vaccine than amongst the non-immunized animals (Group VI).

Mice immunized as described above with a single dose of vaccine (see Tables IV and V) were divided into two groups, A and B. Mice of Group A were sacrificed and exsanguinated two days after they had received vaccine. Group B mice were challenged at that time, together with unvaccinated controls, with results comparable to those shown in Groups II and V in Table IV.

Sera of Group A mice were pooled and tested *in vivo* for protective antibody (North, 1959). As was expected, none was detected. In addition, in-vitro tests failed to reveal antihæmolysin or agglutinin.

Discussion.

The results reported above show that a general immunity against staphylococcus infections follows the injection of a single dose of vaccine in mice similar to that ("interference" effect) described by Evans and Perkins (1954*a* and *b*, 1955) against experimental *H. pertussis* infection in mice.

Like the interference immunity against *H. pertussis* infection, this immunity against staphylococcus infection has the following characteristics: (*a*) it follows a single injection of vaccine (either a bacterial suspension or a cell-free supernatant); (*b*) it develops rapidly and is transient; (*c*) it is not associated with demonstrable protective antibody in the serum; (*d*) it appears to be genus-specific; (*e*) it follows vaccine injected by a different route from that of the challenge injection.

On the other hand, there appear to be some differences which may be more apparent than real. Evans and Perkins (1954*a*) found that the interference effect of pertussis vaccine was not obtained when the vaccine was heated at 100° for 15 minutes. However, staphylococcus vaccine appears to be quite a good interfering agent when boiled for double that time (see Table VI).

As far as we know, non-pathogenic strains of *H. pertussis* have not been isolated from the human respiratory tract. Therefore, we cannot say whether the high degree of interference immunity produced by a harmless *Staph. albus* has its counterpart in the field of *H. pertussis* infection. Our results indicate that the interfering factor is genus-specific, soluble and relatively stable to heat. The fact that it is present in *Staph. albus* is especially interesting and perhaps important. The *Staph. albus* vaccines actually gave better protection than *Staph. aureus* vaccines. This may simply be due to the fact that *Staph. albus* is more rapidly inactivated.

Evans and Perkins (1955) were able with certainty to separate the interference type from the antibody type of immune response, and to show just where the one faded out and the other (the antibody type) appeared.

Using an inactivated (killed) vaccine, we have so far been able to show definitely only the interference type of immunity against infection with the staphylococcus.

In the case of *H. pertussis*, only a few hundred living cells of a suitable strain are required to kill a mouse by the intracerebral route. On the other hand, some millions of virulent living staphylococci in broth culture are required to kill a twenty-gramme mouse by the intraperitoneal route (North, 1959). In spite of this difference, interference immunity appears to play an important part in determining the lethal effect of challenge in both cases. One reason why challenge with a young actively growing culture is best becomes apparent. An older culture contains more dead and effete organisms and, therefore, relatively more of the substance that will induce interference.

Elek (1959), in his monograph "Staphylococcus Pyogenes and its Relation to Disease", makes no reference to the type of immunity described in this paper—a general specific immunity of short duration following one dose of vaccine. He refers at some length, however, to Besredka's "antivirus", which Besredka (1932) stated produced a specific local but not a general immunity. "Antivirus" was a filtrate of a broth culture of staphylococci or other bacteria which, according to Besredka, contained a specific inhibitory substance. Elek (1959) cites many reports, notably that of Mallory and Marble (1925), which tend to disprove Besredka's conclusions.

Our own findings lead us to believe that interference immunity is similar to, if not identical with, Besredka's "antivirus" immunity. However, he was wrong in believing that antivirus produced only a local immunity. It is obvious that his experiments were not suitable for demonstrating a general immunity with protection against a lethal challenge as the criterion of protection. If our interpretation is correct, the interference effect must have a general application in bacteriology.

The interference type of bacterial immunity is probably like the similar phenomenon in animal viruses (Henle, 1950)—cellular in type. If the interfering bacterial cells

TABLE VI.

"Interference" Effect of "Standard" Staphylococcus Vaccine Compared with that of Other Bacterial Vaccines.[1]

Group.	Vaccine Used.	Day of Death after Challenge.	Survivors at Seven Days.
1	"Standard" (S1531).	1 1 1 2 4 5	13/19
2	"Standard" (boiled for 30 minutes).	1 1 1 1 1 1	13/19
3	*Staph. albus* (S805).		19/19
4	Streptococcus.	1 1 1 1 1 1 1 1 1 1 3 3	7/19
5	Nil (controls).	1 1 1 1 1 1 1 1 1 1 2 3	7/20

[1] All groups of mice were challenged simultaneously with S1531 two days after administration of 1 ml. of vaccine subcutaneously, shown in the second column Experiment was terminated seven days after challenge with S1531.

TABLE VII.

"Interference" Effect of Supernatants of Staphylococcus Vaccines.[1]

Group.	Immunizing Agent.	Day of Death after Challenge.	Survivors at Seven Days.
1	Supernatant of "standard" (S1531) vaccine.	4 5 5 6	16/20
2	Nil (controls).	1 1 1 1 1 1 1 2 2 3 3	8/20
3	Whole cell streptococcus (Str. 270) vaccine.	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	1/20
4	Supernatant of *Staph. albus* (S805) vaccine.	1 1 1 1 1 1 1 1 1	11/20
5	Whole-cell "standard" (S1531) vaccine.	1 1 1 1 1 1 1 1 1 1 1 2	8/20
6	Nil (controls).	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	3/20

[1] Groups 1 and 2 refer to one experiment, Groups 3, 4, 5 and 6 to another. Mice were challenged intraperitoneally with strain S1531 two days after immunization of groups vaccinated as shown in the second column. Experiments were terminated seven days later.

or soluble material from them blockade the host cells, interference may be a potent factor in the production or non-production of high titre antisera. The question of spacing of doses of staphylococcus vaccine or other antigen in the production of hyperimmune sera is reopened. Our results (see Table I) make it clear that a slowly developing and durable type of immunity in mice can follow the injection of a vaccine containing living staphylococci. It remains to be proved whether or not similar protection can be afforded with a killed vaccine.

The fact that the inducing (interfering) factor is soluble and common to all staphylococci suggests that it may be a polysaccharide (Keogh, North and Warburton, 1948). Whether this proves so or not, it should be possible to extract the factor in relatively pure from. Such an extract may prove to be a useful prophylactic agent in a ward or nursery where staphylococcal infections are prevalent. Preliminary experiments have already shown that the inducing factor also gives protection against toxin. Therefore, it may also be active as a therapeutic agent.

Summary and Conclusions.

1. A rapidly developed but transient type of specific immunity in mice follows one injection of staphylococcus vaccine. It probably applies to many other—if not all—species of bacteria.

2. This immunity is not associated with the presence of detectable antibody in the serum.

3. It appears to be similar in nature to the interference effect produced by the injection of *H. pertussis* vaccine in mice.

4. It follows the injection of a vaccine consisting of either a bacterial suspension or the filtered supernatant of a bacterial suspension of pathogenic or non-pathogenic staphylococci.

5. Certain possible implications of this type of immunity are discussed.

Acknowledgements.

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PROGNOSTIC SIGNS IN SURGICAL INDUCTION OF LABOUR.

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FEW things are more harassing in obstetrics than the management of the patient in whom surgical induction of labour has failed. If the patient is a multipara whose confinement is overdue by her dates, and if a free flow of amniotic fluid is obtained when the membranes are ruptured artificially, the obstetrician usually feels confident of success; but is his confidence justified? And can these criteria be considered trustworthy guides in practice? In this paper the results of artificial rupture of the membranes in 427 consecutive cases are reviewed. An attempt is made to assess the prognostic value of certain clinical features which may influence the obstetrician in his selection of cases for induction and have a bearing on the success of the procedure.

Method and Material.

The patients were treated in the Nuffield Department of Obstetrics and Gynæcology, Oxford. All the cases were routine ones in which it was thought necssary to induce premature labour for medical reasons. No controlled series was attempted, so some degree of selection must necessarily be present. The cases were, however, all ordinary cases dealt with by ordinary people, so represent the results to be expected from any similar series.

In each case high or low artificial rupture of the membranes was performed, and success was counted if labour began at any time in the subsequent 48 hours. If the interval between induction and onset of labour was greater than 48 hours and the patient had reached the thirty-seventh week of pregnancy, then labour was regarded as spontaneous in onset and the induction was deemed a failure. If, before the thirty-seventh week of pregnancy, labour began within four days of artificial rupture of the membranes, then the induction was counted successful. Defects in documentation account for the missing cases in Tables II, III and IV.

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Results.

The success rate for the whole series of 427 cases in which labour was induced by artificial rupture of the membranes was 85·2%. With low rupture of the membranes (185 cases) the success rate was 94%, and with rupture of the hind waters (236 cases) the success rate was 78%; but as these individual rates were subject to a high degree of selection, they must be discounted. The "whole group" rate only is significant.

TABLE I.
Artificial Rupture of the Membranes, Comparing Success Rate with Parity.[1]

High and Low Artificial Rupture of the Membranes.	Parity of Subjects.		Total.
	Primigravidæ.	Multiparæ.	
Successful cases	158	206	364
Unsuccessful cases ..	28	35	63
Total	186	241	427
Success rate	84·9%	85·5%	85·2%

[1] The standard error of the mean success rate is 1·7%, so the observed differences are not significant.

Parity.

In the whole series, no significant difference in success rates was observed between primigravidæ and multiparæ. In both groups artificial rupture of the membranes met with approximately 85% success (Table I).

Duration of Pregnancy.

After the estimated date of delivery, the success rate of surgical induction of labour was 89%, whereas before that date it was 82%. While the difference can be shown to be statistically significant, it is too small to be of any importance in clinical practice and in all probability is accounted for by the greater likelihood that spontaneous labour will occur once the estimated date has passed (Table II).

TABLE II.
Efficiency of Artificial Rupture of the Membranes, Compared with Duration of Gestation.[1]

High and Low Artificial Rupture of the Membranes.	Duration of Gestation in Weeks.							Total.
	<36	37	38	39	40	41	42+	
Successful cases ..	41	34	61	58	57	61	40	352
Unsuccessful cases ..	8	6	16	12	7	5	7	61
Total	49	40	77	70	64	66	47	413
	84	85	79	83	89	92	85	85·3%
Success rate	82%				89%			85%

[1] No statistical significance can be found in the individual weekly rates by the χ^2 test, but the coarser rates of "before" and "after" the estimated date of confinement can be shown to differ significantly. This difference, though present, is too small to be of much practical importance.

State of the Cervix.

Rather than quarrel with that nebulous characteristic of the pregnant cervix, its ripeness, in this paper the anatomical configuration of the cervix has been classified into the following three groups:

A. The "Favourable" Cervix:
  (i) All cervices dilated to admit three fingers.
  (ii) Those cervices dilated to admit two fingers and well effaced.
  (iii) In primigravidæ, those cervices dilated to admit one and a half fingers, well effaced and soft.

B. The "Unfavourable" Cervix:
  (i) The long cervix, dilated to admit one finger.
  (ii) The tight cervix, dilated to admit one finger and unable to be stretched.
  (iii) The sacral cervix (post-axial).
  (iv) In multiparæ, the thick uneffaced cervix, dilated to admit one and a half fingers.

C. The "Intermediate" Cervix:
  (i) Those cervices not in one of the above-mentioned groups.
  (ii) Cervices incompletely described in the notes, and therefore assumed to be in neither Group A nor Group B.

TABLE III.
Efficiency of Artificial Rupture of the Membranes Correlated with the Anatomical Configuration of the Cervix.[1]

High and Low Artificial Rupture of the Membranes.	State of Cervix.			Total.
	"Favourable."	Intermediate.	"Unfavourable."	
Successful cases	142	157	41	340
Unsuccessful cases ..	6	27	24	57
Total	148	184	65	397
Success rate	96%	85%	63%	85·6%

[1] Application of the χ^2 test shows $P<0·01$, so that the differences observed are highly significant. Similar separate analysis of these rates between high and low artificial rupture of the membranes showed no great variation from the pattern of the combined series.

With the cases classified thus, it was found that at surgical induction of labour the "favourable" group met with 96% success, the "intermediate" group with 85% success and the "unfavourable" group with 63% success (Table III). These differences are not only statistically significant, but are so divergent as to be of considerable practical importance.

TABLE IV.
Efficiency of Drew-Smythe Catheterization Compared with Volume of Liquor Amnii Removed.[1]

High Artificial Rupture of the Membranes.	Volume of Liquor Removed. (Fluid Ounces.)								Total.
	0 to 4	5 to 8	9 to 12	13 to 16	19 to 20	21 to 30	31 to 40	40 and over	
Successful cases ..	15	22	37	26	36	28	9	7	180
Unsuccessful cases ..	2	5	9	4	12	7	7	2	48
Total	17	27	46	30	48	35	16	9	228
	88	81	80	87	75	80	56	78	78%
Success rate	83%				74%				

[1] The standard error of the difference of 83% and 74% is 5·4%, so any observed difference in success rate is without significance.

Amniotic Fluid Removed.

The volume of amniotic fluid removed at high artificial rupture of the membranes (Drew Smythe catheterization) had no bearing on the success rate of the procedure (Table IV). Any differences observed were shown to lack statistical significance.

Discussion.

It may be said at once that from this work the only sign of any practical importance in predicting the outcome of surgical induction of labour is found in the state of the cervix. If the cervix is soft, dilated to admit two fingers and well taken up before artificial rupture of the

membranes is performed, then the risk of the operation is minimal. However, if the cervix is long, firm or tight and barely admits one finger, the urgency of the procedure should be reviewed, and any attempt at surgical induction must be undertaken in the knowledge that labour can be expected to follow within 48 hours in only 63% of cases. Drew Smythe (1949) has stressed the desirability of assessing the state of the cervix before using his methods, and more recently Cunningham (1954), impressed by the importance of the state of the cervix, has described a method of induction of labour which aims at eliminating the more difficult cases by converting a less favourable cervix into a more favourable one. The efficacy of his method is as yet unconfirmed, but his approach to the problem is worthy of serious consideration.

It is widely taught that multiparous patients come into labour after artificial rupture of the membranes more easily than primigravid patients, yet the figures in this series do not support that belief. A number of authors have made similar observations (Bellingham, 1954), and some have even described better results with primigravidæ (Drew Smythe and Thompson, 1937; Tennent, 1938; Tennent and Black, 1954). Despite these findings, the teaching that the converse is true still persists. Is it not time for review?

There is also a general belief that the nearer a patient is to term, the greater the likelihood of success at surgical induction. To a certain extent this is true, and in support it has been found in this present paper that the success rate of surgical induction of labour is higher after the estimated date of delivery than before it. On closer scrutiny, it will be noticed that the actual difference in success rates, though statistically significant, is so small as to be of little clinical importance, and may quite justifiably be discounted in practice.

Lastly, contrary to the belief of Drew Smythe (1949) that success at surgical induction depends in part on the volume of amniotic fluid withdrawn, no similar correlation was found in this series. Labour followed just as well whether 4 or 40 oz. of amniotic fluid were removed. It is also of note that those authors who quote the clinical impression that the more amniotic fluid is removed, the better is the result, have not so far published figures supporting their assertions.

Conclusion.

In assessing the suitability of a case for surgical induction of labour by artificial rupture of the membranes, much greater stress should be laid on a knowledge of the state of the cervix than on any other alleged prognostic factor.

Summary.

Four hundred twenty-seven consecutive cases of surgical induction of labour are reviewed, and the effect of parity, duration of pregnancy, anatomical state of the cervix and amount of amniotic fluid withdrawn on the success rate of the procedure is studied.

Acknowledgement.

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OBSERVATIONS UPON THE DETERMINATION OF SERUM AND URINE CALCIUM WITH THE DYE PLASMOCORINTH B.

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FOR some years, investigations of various aspects of calcium metabolism have been performed in the Clinical Research Unit of the Royal Prince Alfred Hospital, Sydney. Serum calcium concentration has been determined by the method of Clark and Collip (1925), using the wash reagent recommended by Wang (1935); the only disadvantages that we have experienced with this method are that it is rather time-consuming, and that meticulous attention to details of technique is essential. The determination of urinary calcium concentration has offered considerable difficulty, as urine has often had to be preserved for long periods of time, and the addition of any ions that may be of interest in subsequent balance studies has had to be avoided. Accordingly, we have added 4 ml. of glacial acetic acid per 100 ml. of urine as preservative; this has necessitated ashing of the samples to remove acetate before the removal of phosphates, the latter being a necessary step before the precipitation of calcium as oxalate (McRae, Crowe and Dale, 1959). This complicated method has made the measurement of urinary calcium concentration very laborious and inaccurate, and several replicates are necessary with each sample.

The determination of calcium concentration with the disodium salt of the dye, 1-hydroxy 4-chloro 2:2-diazobenzene 1:8-dihydroxynaphthalene 3:6-disulphonic acid (plasmocorinth B—Yanagisawa, 1955; Kingsley and Robnett, 1957) seemed to offer the first direct spectrophotometric method which was technically simple and reliable. We have accordingly compared results obtained with this method and those obtained with our former standard methods, on both urine and serum. The modification of the plasmocorinth B method described by Kingsley and Robnett (1958) has been used.

Materials and Method.

A stock solution of plasmocorinth B is prepared, containing 3·642 mg. per millilitre of the dye. This is diluted 1:50 with 1·0N sodium hydroxide solution immediately before use. To 6·0 ml. of the diluted dye solution, 0·2 ml. of the test solution is added; the mixture is incubated at between 15° and 20° C. for 10 minutes, and then the decrease in optical density at 615 mμ is read against a control containing 0·2 ml. of distilled water instead of the test solution; the density of the control is set at 1·000. The solution is said to give stable readings for 30 minutes, in quartz cuvettes.

Results.

Calcium in Urine.

As shown in Table I, the values obtained for calcium in fresh urine, and in urine preserved with either hydrochloric acid (1·0 ml. of the concentrated acid per 100 ml. of urine) or acetic acid (4·0 ml. of glacial acetic acid per 100 ml. urine), were identical. Also, recoveries of calcium, added as the chloride to essentially calcium-free urine, were quite satisfactory, and they were indeed considerably more accurate than those obtained with the ashing technique previously used.

Calcium in Serum.

The calcium content of 60 consecutive samples of serum was determined by the oxalate-permanganate method of Clark and Collip (1925), and by the dye method. Several of these samples came from a single patient, who was suffering from a secreting carcinoma of the parathyroid gland, and others from patients with carcinomatosis of bone with hypercalcæmia. The mean value was 13·62 mg.

[1] Supported in part by the National Health and Medical Research Council of Australia.

per 100 ml. by the titrimetric method, and 12·65 mg. per 100 ml. by the dye method. For each serum sample, both determinations were performed in duplicate and the mean value was used. For each sample of serum the difference between the two values was calculated, and the mean difference was 0·97 mg. per 100 ml., with a standard error of 0·11 ($P < 0·001$). Nine replicate determinations on a single sample of serum gave a mean of 10·9 mg. per 100 ml. (S.D. 0·3) with the titrimetric method and 9·5 mg. per 100 ml. (S.D. 0·3) with the dye method.

As no such difference was found in the recovery of calcium from standard solutions, it was considered likely that the serum proteins may in some way alter the absorption of light by the dye solution. Accordingly, some calcium-free pooled serum was prepared by dialysis for 24 hours against two lots of 0·01M sodium ethylene diamine tetraacetate—0·15M sodium chloride solution, pH 7·4 at 0° C., followed by three lots of 0·15M sodium chloride to remove the chelating agent. The serum was then clarified by filtration through a Whatman No. 42 paper and stored at 0° C. Titrimetric determination showed a calcium concentration of approximately 0·15 mg. per 100 ml. at this time.

TABLE I.
Accuracy of Dye Method in Measurement of Urine Calcium.

Test Solution.	Calcium Added. (Mg. per 100 ml.)	Calcium Found. (Mg. per 100 ml.)
Fresh urine	0	4·65
Urine *plus* hydrochloric acid ..	0	4·6
Urine *plus* acetic acid	0	4·6
"Calcium-free" urine	0	1·0
"Calcium-free" urine	2·0	3·2
"Calcium-free" urine	4·0	5·2
"Calcium-free" urine	6·0	7·4
"Calcium-free" urine	8·0	9·1
"Calcium-free" urine	10·0	11·0

When we attempted to measure the calcium concentration with the dye method, the optical density was 1·040 with a standard of distilled water and dye set at 1·000—that is, an apparent concentration of −0·6 mg. per 100 ml., or about 0·75 mg. per 100 ml. lower than the true value. As a demonstration of the avidity of calcium-free serum for calcium, some was stored in a glass bottle for a week, after which titrimetric analysis showed a calcium concentration of 0·4 mg. per 100 ml.; with the dye method, the optical density was 1·012, corresponding to −0·2 mg. per 100 ml., or 0·6 mg. per 100 ml. less than the true figure. In both these experiments, the decrease in optical density resulting from the addition of a known quantity of calcium as chloride was the same in the presence and absence of the protein, when measured with the relevant blank. In another experiment, in which the solutions were allowed to stand for a longer period in the cuvettes, there was a gradual increase in the optical density of the solution containing serum plus calcium plus dye from 0·322 to 0·365, corresponding to an apparent decrease in calcium concentration of 0·7 mg. per 100 ml. of serum.

All the foregoing experiment were performed during the summer months; some further experiments during the winter have shown better agreement, and greater stability of spectrophotometer readings.

On the basis of the above-mentioned results, we conclude that the dye method accurately determines the calcium content of urine, either fresh or preserved. However, the method does not determine the serum calcium content accurately, and several sources of error were found, almost certainly due to the presence of protein. Firstly, in the presence of calcium-free serum the optical density of the dye solution was increased, resulting in an underestimate of the order of 0·7 mg. per 100 ml. Secondly, if the determination was not performed rapidly, there was an increase in the optical density of the dye-serum-calcium mixture, leading to an error of the same order and in the same direction. Thirdly, it seems that the ambient temperature had an effect on one or both of these factors, as the errors were larger during the summer; it will be recalled that the method includes a period of incubation between 15° and 20° C., and significant warming up may occur rapidly after placing in the Beckman chamber (which may be as high as 40° C. in summer).

As the serum calcium value in health is relatively constant, and its alteration from the normal is of such great prognostic significance, its determination with accuracy is essential. Therefore, in spite of the advantages of speed and simplicity of the dye method, and of the small serum sample required, we do not recommend its adoption for routine purposes unless adequate checks are made at fairly frequent intervals against a standard method.

Summary.

The calcium concentration in serum and urine has been determined by the plasmocorinth B dye method, and the results are compared with those obtained by oxalate-permanganate methods previously in use in this laboratory. The dye method has been found to yield accurate results in the determination of urinary calcium concentration, but not in the determination of serum calcium concentration. Some of the factors which lead to erroneous results in the latter determination are discussed.

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PULMONARY COMPLICATIONS FOLLOWING GASTRIC SURGERY.

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THE effect of an incision in the abdominal wall in diminishing the mechanical efficiency of respiration has been fully described by Anscombe (1957) and by Anscombe and Buxton (1958), and its importance as a factor in the ætiology of post-operative pulmonary complications clearly established. However, this is only a predisposing factor; other factors must be looked for in the patient himself and in the circumstances attendant upon his operation. In common with Keating and Myles (1957) in Jamaica, we have been impressed by the infrequency of post-operative pulmonary complications under tropical conditions. We therefore made a study of 60 unselected patients undergoing operations for peptic ulcers with a view to estimating the incidence of post-operative pulmonary complications. Gastric operations have been chosen for study because, as Anscombe has shown, an epigastric incision causes a greater diminution of respiratory efficiency than any

other, and is therefore most likely to be followed by chest complications. A study of this kind will not be of much value unless the many factors which may play some part in the ætiology of post-operative chest complications are recorded. These must include the general physical characteristics of the patients under consideration, their smoking habits, the pre-operative condition, the nature and duration of the operations, the anæsthetic given, and the post-operative treatment.

Material.

Sixty patients who consecutively underwent operations for peptic ulcers in one surgical unit at this hospital between July, 1957, and March, 1959, provide the material for this study. All the patients were Asians, but of the three races forming the bulk of the population of Malaya, only Chinese and Indians were represented. There were no Malays, among whom peptic ulcer is most uncommon, as it also is among Asian women, there being only two female patients in this series.

With four exceptions, all the patients were from the poorer sections of a community whose general standard of living is lower than in the west. Most of the patients were undernourished, and many showed obvious evidence of malnutrition and anæmia. The average weight of the patients was only 49 kg. (range 37 to 62 kg.), and the average hæmoglobin value, with the exclusion of the five patients who underwent emergency gastrectomies, was 12·1 grammes per 100 ml. (range 8·8 to 14·4 grammes per 100 ml.), in spite of pre-operative treatment. The average age of the series was 41 years (range 21 to 65 years). Two patients who were aged over 60 years were very frail women.

About one-third of the patients smoked cigarettes, but none more than 20 per day. There were two known pethidine addicts and two opium addicts; but we think there were more of the latter who were reluctant to admit the habit. Thirty-eight patients were considered to be "good risks" (see Table I); these included seven patients with radiological evidence of arrested pulmonary tuberculosis, but all were free of symptoms. The following make up the 22 patients considered to be "fair" or "poor" risks: four with severe acute hæmatemesis and gravely ill; one with a perforated duodenal ulcer; two with moderately severe chronic bronchitis and emphysema; one a worker in a tin-smelting works with pneumonoconiosis; two with severe anæmia (hæmoglobin values of 8·8 and 9·6 grammes per 100 ml. respectively) because of repeated attacks of hæmatemesis and melæna; two frail old women with severe atheroma (one of whom had multiple aneurysms, the other weighing only 24 kg.); ten with general malnutrition.

TABLE I.[1]
Results.

Number of Patients.	Number without Pulmonary Complications.	Number with Pulmonary Complications.		
		Productive Cough.	Atelectasis.	Total.
"Good risk", 38	29 (76% ±6·9%)	7 (18% ±6·3%)	2 (5% ±3·6%)	9 (23%)
"Fair risk", or "poor risk", 22	11 (50% ±10·7%)	8 (36% ±10·3%)	3 (13% ±7·3%)	11 (50%)
Total, 60	40 (67% ±6·1%)	15 (25% ±5·6%)	5 (8% ±3·6%)	20 (33%)

[1] The standard error of each percentage is included.

Method.

For our purpose, we have defined a post-operative pulmonary complication as occurring in a patient who develops a productive cough in the immediate post-operative period. In addition to the routine clinical pre-operative and post-operative examinations, an X-ray film of the chest was taken in the pre-operative period, and another was taken in all cases 24 hours after operation. Nearly all the X-ray films were taken in the radiology department with the patients standing up. Early in the series a few post-operative chest films were taken in the supine position; but the raising of the diaphragm tended to obscure the picture at the lung bases, where post-operative atelectasis almost invariably occurs.

Most of the patients sat out of bed on the evening of the first post-operative day. Instruction was given on breathing exercises for a few days before operation, and these were continued after operation as soon as the patients were sufficiently alert to cooperate. Percussion of the chest was carried out as a routine measure at convenient intervals.

Anæsthesia.

Apart from the five "emergency" patients who were given only atropine, premedication consisted of morphine, 10 mg., and atropine, 0·6 mg., one hour before operation. Induction of anæsthesia was with thiopentone sodium followed immediately by pethidine. Anæsthesia was maintained with nitrous oxide and oxygen (2:1) in a circle absorber with a controlled leak. Suxamethonium was used to permit oral intubation with a cuffed tube, and relaxation was maintained with *d*-tubocurarine. Controlled respiration was used throughout the operation. All the patients received intravenously atropine, 0·8 mg., followed by neostigmine, 2·5 mg., after closure of the peritoneum. In the management of the anæsthesia our policy has been to use a relatively substantial induction dose of thiopentone (250 to 500 mg.), and by the generous use of pethidine to minimize the need for further increments of thiopentone during the course of the anæsthetic. The average dose of thiopentone was 5·3 mg. per kilogram of body weight per hour of operating time (S.D. 1·58). With very few exceptions, patients were sufficiently recovered on leaving the operating theatre to obey simple commands, and were free from pain.

The average operating time was 123 mintues, and the operations performed were as follows: vagotomy and pyloroplasty, seven cases; Bilroth I partial gastrectomy, 30 cases; Bilroth II partial gastrectomy, 23 cases; total, 60 cases.

Post-Operative Sedation.

While it is true that sedation may be of value in the post-operative period, in that coughing is made less painful so that secretions are more readily cleared by the patient, we believe that during the first 24 hours after return to the ward the respiratory depression that results outweighs this advantage. Our policy in this series has therefore been to give morphine only when patients are evidently in pain and becoming restless as a result.

Results.

The results are summarized in Table I. There was no mortality. In all, 20 patients developed pulmonary complications: 15 (25%) had a cough with increased secretions in the post-operative period, and five (8%) had radiological evidence of atelectasis. In three of the latter cases the diagnosis was made on clinical grounds and confirmed by radiography. In the remaining two cases the diagnosis was made only on X-ray films, which showed small areas of atelectasis. All the patients with post-operative atelectasis recovered rapidly with simple physiotherapy; bronchoscopic aspiration was not required.

Discussion.

The special feature of surgical practice in the underdeveloped countries of the tropics is the necessity of performing major operations on many frail, undernourished and anæmic patients. Therefore, in assessing patients from the point of view of anæsthetic and surgical risks, our standards are necessarily lower than they would be with a more robust population. The result of our present

series demonstrates that pulmonary complications are twice as prone to occur in these "fair risk" or "poor risk" patients, who tend to be apathetic and immobile during the early post-operative period, than in the "good risk" patients (see Table I). Nevertheless, the over-all incidence of pulmonary complications in our series is significantly lower than in similar series reported in British patients. Thus, Anscombe (1957) reported the occurrence of pulmonary complications defined as a productive cough after operation in 73% of the 38 patients who underwent gastrectomy. The incidence of a similarly defined complication in this series is 25%.

Radiologically confirmed atelectasis occurred in 8% of patients in the present series, whilst Palmer and Sellick (1953) reported an incidence of 43% in a series of 99 cases, comprising 66 gastrectomies and 24 inguinal herniorrhaphies, in which preventive measures consisted of pre-operative postural drainage and simple physiotherapy. They do not state the incidence in relation to each operation; but, in view of the greater effect of an upper abdominal incision in reducing the mechanical respiratory efficiency (Anscombe, 1957; Anscombe and Buxton, 1958), it seems reasonable to suppose that atelectasis was at least not less frequent among their patients who underwent gastrectomy. On the other hand, Keating and Myles (1957), reporting on a series in Jamaica, comprising 31 gastrectomies and 62 herniorrhaphies, found no case of post-operative atelectasis. We believe that a strict comparison cannot be made because of their practice of taking post-operative X-ray films 36 to 48 hours after operation. In our experience, atelectasis appears most frequently in the first 24 hours. Small areas of atelectasis causing little or no symptoms may clear up within the next 24 hours, and would be missed in a 48-hour post-operative X-ray examination.

Conclusion.

In conclusion, our results demonstrate that the incidence of pulmonary complications, either as post-operative cough with sputum or as radiologically demonstrable atelectasis, is significantly lower than in similar reports from Britain, thus confirming the earlier work of Keating and Myles (1957) in Jamaica. Although Keating and Myles did not give a detailed picture of the patients making up their series, it would seem likely that their series had much in common with ours in Malaya, where climatic and social conditions are rather similar. The outstanding feature of both the Jamaican patients and those of our series is the low incidence of chronic bronchitis as compared with series reported from Britain. Thus, Palmer and Sellick (1952 and 1953) in London found as many as 40% of the patients in their series with a history of chronic bronchitis, as compared with a 3% incidence in our series. We believe that the rarity of chronic bronchitis is the main reason why few of our patients develop pulmonary complications after gastric surgery.

Summary.

A group of 60 patients who underwent gastric operations at the General Hospital, Penang, have been studied with regard to their pre-operative physical state and the incidence of post-operative pulmonary complications. All patients had chest X-ray examinations before and 24 hours after operation. The incidence of pulmonary complications was 33% and of radiologically demonstrable atelectasis 8%. The significance of these findings is discussed.

Acknowledgement.

We wish to thank Dr. Victor Roseverne for his advice regarding the X-ray films.

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Reports of Cases.

SENSITIVITY TO PHENINDIONE ("DINDEVAN"): REPORT OF TWO CASES.

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IN recent years, the use of anticoagulants for long-term treatment has increased. It seems probable that, as reports of the beneficial effects of long-term anticoagulant therapy appear, this increased use will continue. In Australia phenindione ("Dindevan") is the most widely used anticoagulant for both short-term and long-term treatment. This drug is considered by many to be almost free from toxicity, apart from the hæmorrhagic complications of overdosage.

This paper describes two cases of severe sensitivity reactions to phenindione. These cases are reported to draw attention to the fact that this drug may not be as free from toxic reactions as is widely believed, and that these reactions may be severe.

Elkington (1958) has pointed out that a properly controlled long-term investigation of the effect of anticoagulants in cerebral vascular disease has never been carried out. For this reason, it was decided at Greenvale Village for the Aged to study the effect of long-term anticoagulant therapy on the progress of patients who had suffered from a cerebral thrombosis. When the investigation was begun, a group of 30 patients was divided by a random selection into two groups, one of which was given anticoagulant treatment, and the other kept as a control. This number has since been increased by the addition of new cases as they appeared, the total number of patients observed now being 43.

Of those patients, 21 have been receiving treatment for periods varying from eight months to a few days, the majority for more than six months. Two of this group have developed toxic reactions, one after 36 days' treatment, the second after treatment for 66 days.

Case 1.

A single woman, aged 68 years, was a diabetic of 15 years' standing who had suffered from angina pectoris for some years, and who had, at the time of starting on the trial, made an almost complete recovery from right hemiplegia due to a presumed cerebral thrombosis three years earlier. There was no history of any previous allergic episodes. She was receiving insulin, vitamin supplements, trinitrin and pentaerythritol tetranitrate.

Anticoagulant therapy was instituted, and a satisfactory prolongation of prothrombin time was achieved with the use of phenindione in doses averaging 50 mg. a day. On the thirty-sixth day of the treatment, after a prodromal period of some three days' malaise and anorexia, she developed a rash over the lower limbs, the main element of which was a series of purpuric spots, but which had in addition a background of brownish macules. It appeared very similar to the rashes seen in cases of sensitivity to carbromal (Borrie, 1955). At the time of appearance of this rash, the patient became pyrexial, and her temperature reached 101·8° F. The condition was thought to be a drug sensitivity of some form. By the next day, she had developed a generalized itchy red papular rash, and she had now become very drowsy. All

treatment was suspended, and her insulin was altered to another brand. Nevertheless, her condition continued to deteriorate; the rash extended until it became complete exfoliative dermatitis, most severe on the exposed areas. Her face became very swollen and her eyes puffy. In spite of this, her diabetes remained well under control. On the fourth day after the rash appeared, she was given promethazine ("Phenergan") in a dosage of 25 mg. three times a day without benefit. On the fifth day she was noticed to be jaundiced, and her liver was tender and palpable three fingers' breadth below the right costal margin. The urine was very dark, containing much bile, urobilinogen and bile salts. Over the next three weeks she made a very slow recovery without further treatment, her temperature not returning to normal until 20 days from the time of appearance of the rash. Finally, she recovered completely. Six weeks later, the patient was started on therapy with warfarin ("Marevan"), and has since remained very well.

Many investigations were undertaken. Those of significance include the following. On the sixth day, a blood count gave the following information: the hæmoglobin value was 13·9 grammes per 100 ml. (94%), and the leucocytes numbered 5000 per cubic millimetre, 23% being neutrophils, 72% lymphocytes, 1% monocytes and 4% stab cells. The blood picture showed neutropenia, with a number of atypical but not primitive lymphocytes. On the tenth day the hæmoglobin value was 13·4 grammes per 100 ml. (91%), the leucocytes numbered 6000 per cubic millimetre and the film was normal. On the tenth day also, the serum protein content was 5·9 grammes per 100 ml. (albumin 4·0 grammes, globulin 1·9 grammes), the serum alkaline phophatase content was 22 units, the cephalin flocculation test produced a negative result, the serum bilirubin content was 1·1 mg. per 100 ml., and the Fouchet test produced a positive result. On the seventeenth day the serum protein content was 6·7 grammes per 100 ml. (albumin 4·2, globulin 2·9), the serum alkaline phosphatase content was 12 units, the cephalin flocculation test produced a negative result, the serum bilirubin content was 0·7 mg. per 100 ml., and the Fouchet test produced a positive result.

Case II.

The second patient was a single woman, aged 73 years, who had had a sudden episode of aphasia associated with mental impairment about eighteen months prior to the commencement of treatment. There had been almost no recovery from this attack. As far as could be ascertained, there was no history of previous episodes of hypersensitivity. In addition to phenindione, she was receiving chlorothiazide therapy for mild heart failure. This patient proved somewhat more resistant to phenindione therapy, requiring a dosage of about 100 mg. per day to cause a satisfactory lengthening of prothrombin times. After 66 days on anticoagulant therapy, she developed severe stomatitis, with bleeding from the mouth. The next day, she developed a punctate erythematous rash on her arms and legs, and its similarity to that occurring in the earlier case was at once noted.

Medication was at once stopped, and the patient began to improve. Three days later, phenindione was given for four days, after which the rash extended, and she also developed generalized exfoliative dermatitis associated with some pyrexia. Prednisolone (20 mg. per day) and promethazine (25 mg. per day) were given, and her condition rapidly improved, returning to normal in 14 days.

This patient at no time showed any evidence of liver damage. She had mild pruritus for a short period. A blood count on the fourteenth day, eight days after the last dose of phenindione, gave the following normal findings: the hæmoglobin value was 97%; the leucocytes numbered 8000 per cubic millimetre, 85% being neutrophils, 1% stab cells, 4% eosinophils, 7% lymphocytes, and 3% monocytes.

This patient also has since been given therapy with warfarin, so far without ill effect. She has also been given further chlorothiazide with no recurrence of her rash.

Discussion.

The rash in these two patients was almost identical, and it would appear that they were suffering from the same condition. It seems probable that the underlying cause was a toxic reaction to phenindione for the following reasons: (*a*) phenindione was the only drug which they were taking in common at the time; (*b*) the patient's condition deteriorated rapidly when the drug was recommenced in Case II; (*c*) the clinical features of both cases correspond very closely to descriptions of reactions previously ascribed to phenindione therapy.

From a consideration of these cases and those in the literature, there appear to be four main manifestations of phenindione toxicity: (*a*) fever, which has been seen in all severe cases, including the two described above; (*b*) blood dyscrasias, found in eight previously reported cases and in Case I of this report; (*c*) a rash noted in five of the cases reported by Burns and Desmond (1958), and seen in both Cases I and Case II. This has been briefly mentioned in other reports (Soulier and Gueguen, 1947; Breneman and Priest, 1955); (*d*) jaundice—mentioned in three earlier reported cases (Makous and Van der Veer, 1954; Burns and Desmond, 1958; Kirkeby, 1954), and seen in Case I. These manifestations may be present singly or in combination; in those cases reported in detail, there has usually been more than one manifestation present at a time.

The rash was the most impressive feature of the two cases reported here. It was not absolutely identical in the two cases, but there were many features common to both of them; these were the scarlatiniform appearance of the rash in its early stages, its rapid progression through a morbilliform stage to one of generalized erythema with exfoliation, the gross swelling of the face and neck, and especially the greater severity on the exposed areas.

The first patient had purpura and severe pruritus, which have been reported as features of this condition, and the second had severe stomatitis, which has also been noted in other cases.

The jaundice in Case I was mild and non-specific, later in appearing than the other manifestations, and associated with a raised serum alkaline phosphatase level and normal results from flocculation tests. It thus appears to be similar to chlorpromazine jaundice. This was a feature of the much more severe case of Burns and Desmond. It is worth noting that, during phenindione therapy, the urine is often orange-red in colour, and thus may be mistaken for blood or bile in the urine. This colour is seen more especially in alkaline urine, and is due to breakdown products of the drug.

Blood disturbances in these two cases were not prominent. It is probable that, had a closer watch been kept, more definite changes would have been found. In point of fact, they proved of no significance here, though in another report agranulocytosis appears to have been responsible for the death of a patient (Brown and McMillan, 1954).

It appears that sensitivity reactions to phenindione are rare, since the number of reported cases is very few, despite the fact that the drug is very widely used. In a very complete survey of the literature, Burns and Desmond (1958) were able to collect reports of seven severe cases and added one of their own; they mention five milder reactions. The manufacturers of the drug, when approached, stated that they were aware of only 14 cases. However, many mild reactions cannot have been reported in detail, since Paul Wood (1957) mentioned briefly two cases within his personal experience, and the report on long-term anticoagulant therapy by the Medical Research Council of Great Britain (1959) gives sensitivity to phenindione as a reason for withdrawal from the trial in two of the cases. Thus it would appear that mild sensitivity reactions to phenindione may not be excessively uncommon.

Nineteen patients in this series have now been observed over periods ranging from three to eight months on long-term phenindione therapy, and no further evidence of drug reaction has been seen. In view of the enormous number of patients receiving phenindione therapy without untoward reactions, it must be emphasized that severe sensitivity reactions are extremely rare, and that the association of two cases in this small series is no more than fortuitous. Most courses of anticoagulant therapy are very short, 28 days being about the usual length. It is interesting to note that, had therapy been given only for this length of time here, neither of these cases would have occurred, while six of the eight severe reactions mentioned in the literature occurred after three weeks' treatment. It is conceivable that, with the more frequent use of phenindione for long-term therapy, reactions of the type reported will be seen somewhat more often.

Lastly, it should be emphasized that in this investigation phenindione has been found an eminently safe and satisfactory drug for use in anticoagulant therapy, and that in neither of the cases reported here is the patient in any way the worse for the severe sensitivity reactions experienced.

Summary.

Two cases of severe drug sensitivity reaction are described, which appear to have been due to long-term use of phenindione ("Dindevan") as an agent for anticoagulant therapy. The main features of this reaction are exfoliative dermatitis, blood dyscrasias, fever and jaundice.

In one case all these features were present; in the other the picture was incomplete.

Severe sensitivity reactions attributed to phenindione have been reported very infrequently, although mild reactions may not be excessively uncommon.

Acknowledgements.

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PUNCTURE WOUND OF THE LIVER BY STINGRAY SPINES.

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Clinical Record.

THE patient, Kuabuso, a native male child, aged about seven years, was admitted to the Talasea Hospital on July 3, 1959. Twenty-eight hours previously he had been walking along the beach near his village when he saw a large fish floundering in the shallow water. Thinking it would make a valuable addition to the evening meal, he threw himself upon it and carried it to the beach. It was then discovered that the fish was, in fact, a medium-sized stingray, which had struck him in the abdomen with its spines. The spines broke off flush with the skin. He said that he did not notice any pain at the time. He was taken to the nearby Methodist Mission hospital, where the sister in charge soon found that any attempt to remove the spines was attended with much bleeding. The mission spoke by radio with this station, and the following morning the station workboat was sent to bring the patient to this hospital.

On admission to hospital, he was found to be moderately shocked with a weak, rapid pulse, cold extremities and mental confusion. Unfortunately, our only sphygmomanometer was away being repaired at the time. His temperature was normal. There were two puncture wounds about three-quarters of an inch apart, in the same horizontal plane, just below the right costal margin and just lateral to the tip of the ninth costal cartilage. The outer ends of the two spines were clearly visible in these puncture wounds, and could be seen to move up and down with respiration. The abdomen was extremely tender all over, with guarding, but was not absolutely rigid. Peristalsis was present.

The patient's blood group was determined and a native medical orderly donor was chosen and his blood was cross-matched. The patient was then given 500 ml. of blood while preparations were being made for operation. He was also given 1,000,000 units of crystalline penicillin, vitamin K by intramuscular injection, 3000 units of tetanus antiserum, and premedication with one-twelfth of a grain of morphine and one one-hundredth of a grain of atropine.

His condition improved during the transfusion, and operation was undertaken at once. The anæsthetic used was ethyl chloride and "open" ether given by the European medical assistant. The abdomen was opened by a right subcostal incision below the puncture wounds. The findings were as follows: There was a considerable quantity of liquid and clotted blood in the peritoneal cavity, most of which had gravitated to the pelvis. The two spines had entered the right lobe of the liver about 1·5 inches from its lower border. The direction of the spines was upwards and backwards. The tip of the more medial spine could be palpated through the inferior surface of the right lobe about one-quarter of an inch to the right of the bed of the gall-bladder. The medial spine was embedded 4 in. into the liver substance. Bleeding from the wounds in the liver had ceased. Both spines were then pulled out of the liver by the way they had entered. This required considerable force. Because of the recurved barbs they could not be pulled out through the abdominal wall wounds, and their points had to be delivered through the main incision to make it possible to remove them. The forceful removal of the spines caused fairly brisk bleeding from the wounds in the liver. This stopped after prolonged squeezing of the area involved between fingers and thumb. The blood was mopped out of the peritoneal cavity, and the abdomen closed with drainage by corrugated rubber through a stab wound.

Crystalline penicillin was given after operation, and the drain was removed on the second day. Recovery was uneventful, apart from a superficial wound infection of the puncture wounds and the main incision. An attack of malaria also occurred, and was cured with quinine given by intramuscular injection. The patient was discharged from hospital one month after his admission.

The two spines were 4 in. and 3 in. long, and profusely barbed along both borders with needle-sharp recurved barbs.

Comment.

It would be interesting to know whether more or less bleeding would have occurred from the liver at operation if the barbed spines had been pushed right through the liver and out through the inferior surface instead of being withdrawn by the way they had entered. Other stingray

spine injuries I have seen here have all been in the legs, and all were accompanied by excruciating pain. The patient in this case experienced no pain at all.

Stingrays that I have seen in Australia had only one spine. The natives say that stingrays found in these waters have at least two spines and often more.

Summary.

An unusual injury to the liver by barbed stingray spines and the subsequent clinical course are described.

FULL-TERM TWIN PREGNANCY—ONE FŒTUS IN THE UTERUS, THE OTHER IN THE ABDOMINAL CAVITY—IN A NEW GUINEA NATIVE WOMAN.

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A FULL-TERM abdominal pregnancy is a rare condition. A full-term twin pregnancy, with one fœtus in the uterus and the other one in the abdominal cavity, appears to be a still rarer condition, and the following case report may be of some historical interest.

Clinical Record.

On October 16, 1958, a radio message was received from Lufa that there was some trouble with a woman who had given birth to a child some days previously and now needed attention, as there were some signs that a twin baby had not yet been delivered. On her arrival at the Goroka Native Hospital, the following history was obtained. On October 10, the patient had given birth to a normal mature baby weighing 5 lb. 10 oz. The placenta had been delivered normally and there had been a moderately severe post-partum hæmorrhage. However, the patient did not feel well after the confinement, and four days later she visited the local aid post. From there, two days later, she was transported to Lufa and then on to Goroka.

The patient was examined at 8 p.m. on October 16 at the Goroka Native Hospital with the following findings. She was approximately 30 years old and moderately exhausted after the long journey. Her abdomen was grossly distended, tense and tender; a tumour was visible in the left pelvic area and another just over the symphysis. Her bladder was catheterized and some 30 oz. of urine were removed. The tumour from the left pelvic area became movable and settled in the suprapubic area. There was moderate discharge of lochia. On vaginal examination, it was established that the tumour was a partly involuted uterus. The cervix was dilated sufficiently to admit one finger. No second cervix or uterus was palpable. Insertion of a vaginal speculum confirmed the foregoing findings. The abdomen was much distended and tender, and another hard tumour was palpable in the right hypochondriac area. As there were no signs of an acute abdominal emergency, the patient was allowed to rest till the next morning.

On reexamination of the patient, it was established that the tumour in the right hypochondriac area resembled a fœtal head, with the body in a transverse position in the epigastric region. X-ray examination confirmed this finding. No fœtal heart sounds were heard, no fœtal movements were felt, and the patient herself said that she had not felt any movements. As the patient had some irregular rise in temperature and her hæmoglobin value was 10·5 grammes per 100 ml., operation was postponed, there being no signs of acute distress or a living fœtus. After several blood transfusions and antibiotic therapy had been given, the patient was well enough to undergo an operation on October 22.

Laparotomy was performed by Dr. J. N. R. Crawford through a right oblique incision in the upper part of the abdomen. The peritoneum was thickened and dark. When the peritoneal cavity was opened, a full-term dead fœtus was removed. The skin was macerated and peeling off on touch. The membranes were adherent to the anterior and lateral abdominal wall, the omentum, the ascending colon and the liver. The placenta, which was adherent to the postero-lateral part of the abdominal cavity, was also removed. There was moderately severe bleeding, but it was controlled by ergometrine given intravenously and "Pitocin" given subcutaneously. To avoid any further hæmorrhage and possible damage to the abdominal organs, the rest of the membranes were not removed, the incision was closed and a large drainage tube was inserted. The wound suppurated for a month and continually discharged necrotic material, but closed eventually by the end of December, 1958.

Comment.

Unfortunately, at the time of operation, to avoid any risk to the life of the patient, it was not possible to determine whether this extrauterine pregnancy was a primary abdominal pregnancy, or a secondary one, following tubal pregnancy with secondary abdominal implantation resulting from tubal rupture. As far as it was possible to obtain any reliable information from the patient herself, there was nothing in the history to suggest tubal pregnancy. As the fœtus was a full-term one and died, probably at the time of the delivery of the first baby, and as the membranes were intact, it is more likely that this was a primary abdominal twin pregnancy.

Acknowledgement.

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Reviews.

Mental Symptoms in Temporal Lobe Epilepsy and Temporal Lobe Gliomas: With Special Reference to Laterality of Lesion and the Relationship between Handedness and Brainedness. By Torsten Bingley; 1958. Acta Psychiatrica et Neurologica, Supplement 120, Vol. 33. 9½" × 6¼", pp. 164, with 15 tables. Price not stated.

THE appearance of this monograph is further proof of the present popularity of the temporal lobe among psychiatrists, and of the concomitant attempt—a very laudable one—to break down the brain-mind barrier. This particular contribution comes from the reliable "stable" of the Stockholm Serafimerlarettet, which can boast of such world-wide figures as Olivecrona, Luft, Ekbom and Nils Antoni. The author describes a planned investigation, which occupied him from 1952 till 1955 and involved the collection and detailed study of 90 cases of temporal lobe epilepsy, including 16 cases of temporal glioma. Such numbers are not overwhelming, but the criteria of selection—the presence of epileptic seizures and the presence of a temporal electroencephalographic focus—are different from those of other series. The electrophysiological investigations would seem to be up to the standard of the best centres. A battery of psychological tests was administered; unfortunately, some of the tests used have not been adequately standardized.

The author reviews the semiology of temporal lobe epilepsy, and rightly gives a warning against confusion between clinical and electrophysiological concepts. His own classification is in line with those of Penfield and Jasper and of Gastaut.

An interesting chapter considers the question of handedness and brainedness, giving a critical view of the literature. The author provides an operational definition of sinistrality, and rightly points out the difference between ambidexterous subjects and those of indeterminate handedness. Most of the former are probable sinistrals, while most of the latter are likely to be right-handed. Every one of his series could be classified as either right-handed or left-handed. Brainedness could then be determined with 99% accuracy in dextrals (dominance being in the contralateral hemisphere), but in only 50% of the sinistrals (half the subjects showing crossed dominance).

The author makes a welcome clear-cut distinction between ictal and interictal mental symptoms. His interest is not so much in the detailed phenomenology of psychiatric symptoms as in their relation to cerebral dominance. For this purpose he draws on a series of 253 cases of temporal gliomas not studied personally to swell his numbers. The relationship between lesions of the dominant temporal lobe and mental disturbances is very striking. It affects orectic as well as cognitive functions, and is in substantial agreement with the findings of Meyer and Yates reporting on the Maudsley series.

The bibliography is reasonably extensive. There is no index.

A Short Textbook of Radiotherapy: For Technicians and Students. By J. Walter, M.A., B.M. (Oxfd.), M.R.C.P. (Lond.), F.F.R., D.M.R.E. (Camb.) and H. Miller, M.A., Ph.D. (Camb.), F.Inst.P.; second edition; 1959. London: J. & A. Churchill Limited. 9" x 5½", pp. 540, with 303 illustrations. Price: 56s. (English).

THE first edition of this textbook appeared ten years ago, and immediately earned its place as the most useful text in its field. In the intervening years major developments in radiotherapeutic practice have occurred, so the book has largely been rewritten, many new chapters have been added and it is now "up-to-the-minute".

The authors have accomplished a most praiseworthy job. The fields of radiation therapy and investigation have been completely covered to the standard required. The writing is lucid and easily understood. The explanatory footnotes giving the roots of all technical and medical terms used will be greatly appreciated by students, and form a striking feature of the book. Throughout the work, emphasis has been placed on the principles rather than on the details of techniques described; all the standard procedures have been given proper mention, and care has been taken to point out the advantages and disadvantages of alternative methods.

Only two minor matters for complaint were noted: more useful descriptions and diagrams of the workings of conventional and high-voltage therapy equipment would be appreciated, while in the section on pathology an explanation of the fundamental differences between squamous and basal cell cell carcinomata is needed.

So much good work has been put into the compilation by the authors with such excellent result that it is almost pedantic to make minor criticisms. They deserve the grateful thanks of all radiotherapy technicians and students, who are extremely fortunate to have such a fine textbook.

Total Surgical Management. By J. D. Hardy, M.S., M.D., F.A.C.S.; first edition; 1959. New York and London: Grune & Stratton. 9" x 6", pp. 298, with illustrations. Price: $9.50.

ALL surgeons, general or otherwise, would greatly benefit by studying this book, which contains much that is usually passed on by word of mouth; and it is pleasing to discover good English in the text. This being so, the mention of a "Witzeled-in tube" comes as a surprise, as does the statement that "when possible, the patient's wishes regarding the type of anæsthesia to be employed should be respected, particularly if he is adamant". On a more serious note, the admission is made that "the incidence of complications reported from the large, highly specialized private clinics by no means reflects the general level of surgical practice in the United States", and a warning is given that in other hands the incidence of serious post-operative complications may be much higher.

An attempt has been made to keep this book within reasonable limits; but the price is still rather high. A wide variety of subjects dealing with pre-operative and post-operative care is included; but, of necessity, some of the chapters are little more than summaries. The few references at the end of each chapter contain more monographs than articles. Most of the illustrations are excellent, but a few do not reach this standard.

The management of general surgical conditions is well covered, and attention is especially directed to common lesions and common complications. Even so, it is strange that any discussion of bilateral adrenalectomy and oophorectomy in the management of advanced mammary cancer is omitted. On the other hand, adrenalectomy for adrenal tumours and for adrenocortical hyperplasia receives attention; but, even then, the pre-operative and post-operative régime for patients having total adrenalectomy is not described.

It is, of course, to be expected that no one surgeon would agree with all that is written in a book of this nature, but special reference must be made to a few statements with which the majority would disagree. For instance, it is stated that most patients will survive prompt drainage of a perforated duodenal stump complicating a gastrectomy, that 6 litres of fluid may be given intravenously in the 12 hours prior to operation for an acute pyloric obstruction (in the adult), that catheter suction (and not the immediate use of an adherent bag) is the best way of dealing with a newly-formed ileostomy, and that the best results are often obtained by suturing together the cut ends of the external sphincter muscle after excision of an anal fistula. Primary closure of the wound after excision of a pilonidal sinus is preferred, and it is confidently stated that few of these wounds fail to heal *per primam*. Most surgeons would also not agree with the statement that "it is valuable to irrigate the peritoneal cavity with copious quantities of saline solution if strangulation obstruction is present". After thyroidectomy it is recommended that the wound be drained in most cases; that is good, safe advice, but it is not usually adopted by experienced surgeons.

However, these points are mainly differences of opinion and do not detract from the excellence of this book, which is full of common sense. It is certainly worthy of a place in hospital libraries, and of study by all who are concerned with the treatment of surgical patients.

Midwifery (A Textbook for Pupil Midwives). By Gordon W. Garland, M.D.; 1959. London: The English Universities Press, Limited. Melbourne: G. Malcolm Titt. 8½" x 5", pp. 330. Price: 39s. 6d.

This short textbook for obstetric trainee nurses (290 pages) is surprisingly good. It is well printed on good paper and has a refreshingly different presentation. There are many line diagrams to illustrate the text. The key words are in heavy type to facilitate rapid revision or location of subject matter. There is a very good glossary of obstetric terms, and the presentation throughout is clear and accurate and always has an emphasis on the practical side of obstetrics. Great care is devoted to the teaching of the normal in pregnancy; students often fail to understand the normal in their search for the rare.

There is excellent basic teaching in the physiology of pregnancy and on ante-natal care and diseases associated with pregnancy. The details of the nurse's duties in the management of each stage of labour are given, and the chapters on trial of labour in disproportion and management of the occipito-posterior presentation are excellent.

This short book contains a great deal of very sound and up-to-date obstetric teaching, and, being a new book, it does not suffer from the impediments of a previous edition. It is to be sold well within the price range of nurses in training, and can be strongly recommended for all teaching hospitals as a supplement to their lectures, or as their major textbook.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Sex Differentiation and Development: Proceedings of a Symposium held at the Royal Society of Medicine, Wimpole Street, London, on 10 and 11 April, 1958", Memoirs of the Society for Endocrinology, No. 7; 1960. London: Cambridge University Press. 9½" x 7¼", pp. 199, with many text-figures. Price: 45s. (English).

"Diabetes: With a Chapter on Hypoglycemia", by 54 authors, edited by Robert H. Williams, M.D.; 1960. New York: Paul B. Hoeber, Inc. 9¼" x 6", pp. 816, with 192 illustrations. Price: $20.

"Essentials of Fluid Balance", by D. A. K. Black, M.D., F.R.C.P.; second edition; 1960. Oxford: Blackwell Scientific Publications. 8¾" x 5½", pp. 148, with 6 illustrations and 6 tables. Price: 20s. (English).

"Surgical Nursing and After-Treatment (Darling)", by T. Edward Wilson, M.D., M.S., M.Sc. (Melb.), M.R.A.C.P., F.R.C.S. (Eng.), F.R.C.S. (Edin.), F.A.C.S., F.R.A.C.S.; eleventh edition; 1960. London: J. & A. Churchill, Limited. 8½" x 5½", pp. 628, with 361 illustrations. Price: 30s. (English).

The Medical Journal of Australia

SATURDAY, JUNE 11, 1960.

THE HORMONE TREATMENT OF BREAST CARCINOMA.

THE endocrinological approach to the management of disseminated carcinoma of the breast is a subject about which a great deal has been written, but on which there is no general agreement. According to B. A. Stoll,[1] the first report of the use of testosterone for the control of metastatic cancer of the breast was published in 1939, but the widespread use of androgenic and œstrogenic hormones in this condition was still a new development when the Therapeutic Trials Committee of the American Medical Association undertook, in 1947, to sponsor a cooperative investigation of the effects of steroid hormones in the treatment of advanced mammary carcinoma. The subcommittee appointed to coordinate this investigation suffered a severe setback through the death of the two men who originally headed the project, but in 1956 it was reconstituted, under the chairmanship of Ian Macdonald, as the Subcommittee on Breast and Genital Cancer. This subcommittee has now published its final report[2] on the project begun in 1947, and its findings must be regarded as an authoritative contribution to the problem of the hormone treatment of breast carcinoma. The material for this study consisted of the pooled data of 60 different investigators. This cooperative study was a pioneer project of its kind, and for this reason ran into various difficulties which have provided useful lessons for similar investigations in the future. Reports were received on almost 2000 cases, but for various reasons only 944 of these could be accepted for final analysis. Some of the original objectives of the investigation were found to be impracticable within the framework established. However, the care which has been bestowed on the final evaluation of the results guarantees the importance of the conclusions which emerge. A useful ancillary to the report itself is the guest editorial by Macdonald,[3] in which the conclusions of the report are digested, and which appears in the same issue of *The Journal of the American Medical Association* as the report of the subcommittee. Another useful commentary on a group of results which are now included in this report is to be found in an earlier paper by E. F. Lewison, F. H. Trimble and R. S. Ganelin of Johns Hopkins University.[4]

[1] MED. J. AUST., 1959, 1:70 (January 17).
[2] *J. Amer. med. Ass.*, 1960, 172:1271 (March 19).
[3] *J. Amer. med. Ass.*, 1960, 172: 1288 (March 19).
[4] *J. Amer. med. Ass.*, 1956, 162:1429 (December 15).

The report plainly indicates that some prevalent ideas about the hormone treatment of breast cancer are erroneous. The concept of "hormone dependence", as commonly construed, appears to be at best a doubtful guide. It is true that patients with breast cancer may be divided into the majority who do not respond to hormone therapy and whose expectation of survival is on the average less than 12 months from the appearance of metastases, and a minority who do respond and whose expectation of survival is very much better. There appears to be no means of distinguishing one group from the other except by trial and error. Probably the most important conclusion is that œstrogens are superior to androgens in the treatment of disseminated mammary carcinoma. It is admitted that œstrogens exhibited before the menopause may cause exacerbations of tumour growth, but the proportion of patients in this group who respond even to androgens is only 20%. In the group for whom treatment was instituted within four years after the menopause, a larger proportion of patients responded to androgens than to œstrogens, but this proportion was in both cases low, and the difference was not significant. In all later age groups a higher percentage of patients responded to œstrogens than to androgens. Macdonald dismisses as a myth the "supposed superiority of androgens for skeletal metastases" and comments that "the best that one can say for this whimsy is that only in bony deposits did the androgens approach the effectiveness of œstrogens". It is implied throughout the report that in the older age groups the influence of androgens and œstrogens is qualitatively similar—in other words, that patients who are "responders" may respond either to androgens or to œstrogens, though direct evidence on this point is not brought forward. One of the most instructive comparisons was that between those treated by œstrogens and those treated by androgens in the group whose menopause had occurred spontaneously before treatment was instituted. The two groups were of approximately the same size, and of the combined total (392) 28% were responders and 72% were unresponsive to hormone treatment. Among those who failed to respond, length of survival was almost identical whether androgens or œstrogens were employed. Forty out of 194 patients treated with androgens showed regression of their lesions, while 71 out of 198 of those treated with œstrogens responded. Further, among the responders, the average survival (27 months) of those treated with œstrogens was significantly longer than the average survival (20 months) of those treated by androgens. Macdonald blames the concept of "œstrogen dependence" for the therapeutic neglect of œstrogens in this condition.

An incidental result of this investigation was the discovery of a special group of patients in whom the disease ran a highly distinctive course. This group comprised those who received treatment for the primary tumour before the menopause, then went on to a natural menopause and subsequently developed metastatic lesions. These patients were characterized by a remarkably long latent period (free interval) between the treatment of the primary disease and the development of metastases. The mean free interval in patients who received primary treatment and developed metastases before the menopause

was 21·4 months; the mean free interval of the special group was 87 months; and the mean free interval in patients who received primary treatment after the menopause was 39·2 months. The existence of this special group is important, not only from the point of view of individual prognosis, but because its recognition is important in the evaluation of statistical results.

It is not necessary to discuss here the further detailed comparisons in this report, interesting though some of these results are. As has already been pointed out, this investigation was begun at a time when hormone treatment of advanced carcinoma was still on very uncertain ground. Since then interest has moved to more radical approaches to the problem—oophorectomy, adrenalectomy and hypophysectomy; and the development of improved hormone preparations and new cytotoxic (chemotherapeutic) agents has greatly broadened the possible lines of attack. However, hormonal treatment still has an important place in the management of advanced mammary carcinoma, as may be seen from the article by Victor Stone on the palliative treatment of breast cancer in our issue of May 21,[5] in which this question is discussed with particular reference to the policy adopted at the Austin Hospital in Melbourne. If Stone's statement as to the proportion of patients whose symptoms may respond to endocrine treatment appears optimistic beside the American results, this is at least partly accounted for by the strict criteria of regression employed in the latter investigation, in which no cognizance was taken of merely symptomatic relief. The American investigation establishes some important basic statistics, and it is to be hoped that in due course these will be elaborated by further studies, similarly widely based.

MEDICAL ASPECTS OF ADVERTISING.

MOST thoughtful citizens, and certainly those with a medical training, must be disturbed at times by advertisements with medical implications on radio and television and in newspapers and periodicals. The most obvious type of advertisement in this class is that dealing with the patent medicine group of products, but the field can be extended much more widely to include advertisements for cosmetics, foodstuffs and a variety of other things. Indeed, the latter group is possibly more important because official control is already exercised over advertisements on radio and television relating to "medicine", and more responsible newspapers and periodicals impose certain standards on their advertisers.

As it stands at present, the Commonwealth *Broadcasting and Television Act* states that a licensee shall not broadcast or televise an advertisement relating to medicine unless the text has been approved by the Director-General of Health or, on appeal, by the Minister for Health. This is useful but too limited in its scope. It is gratifying therefore to note that the National Health and Medical Research Council at its recent meeting in Canberra adopted a recommendation that the Commonwealth Government's authority to supervise radio and television advertisements for medicines and medical preparations be widened by a clarifying amendment of the *Broadcasting and Television Act*. The suggested amendment would mean, first, the substitution for the word "medicine" of the words "a substance or appliance for which a therapeutic use is claimed", and second, the addition of the words "a substance, appliance, method or technique for which cosmetic, physiological or anatomical advantages are claimed". A "therapeutic use" is described as "a use for the purpose of preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury, or influencing, inhibiting or modifying a physiological process". The amendment seems reasonable. It does not mean suppression of legitimate advertising but would ensure control that would be in the public interest. The existing powers are exercised with fairness and common sense, and no honest advertiser should have cause to object to the suggested extension.

The National Health and Medical Research Council also recommended that, in consultation with publishers and advertisers, steps should be taken to draw up a uniform code for the advertising of the substances and appliances mentioned, for submission to the Council's next meeting. If this means an effort to draw newspapers, journals and the like into a mutually acceptable scheme for the protection of the public against the exaggerated, misleading and even dangerous claims sometimes made in advertisements relating to matters of health, the move is to be heartily applauded.

[5] MED. J. AUST., 1960, 1: 798 (May 21).

Current Comment.

MEDICAL EXAMINATIONS FOR DETECTION OF CANCER.

The following statement is published in the Monthly Paper of the Victorian Branch of the B.M.A., No. 27, May, 1960. It was prepared after representatives of the Branch Council and of the Anti-Cancer Council of Victoria had discussed the problems associated with medical examinations for detection of cancer. Although in some of its details it applies specifically to Victoria, it is in general a thoughtful statement of the position as it applies throughout Australia. We have therefore taken the liberty of passing it on for the information and consideration of the profession generally.

> Now that increasing numbers of people are becoming cancer conscious, requests are frequently made for doctors from persons wishing a medical examination for detection of cancer. Letters published in the press, and statements made to officers of the Anti-Cancer Council of Victoria, indicate that some medical practitioners are reluctant or unwilling to make such examinations of persons in apparent good health.
>
> The Anti-Cancer Council in its educational campaign has not advised a healthy individual to seek such an examination. The Anti-Cancer Council's policy is to spread knowledge of the common warning signs of cancer, and to advise any person noting one of the warning signs to visit his own doctor for further advice.
>
> However, in other countries and particularly in North America, cancer organisations often advise a medical-check up for detection of cancer yearly, or more frequently. Many persons in Victoria, aware that such advice is sometimes given in U.S.A. and Canada, desire such examinations.
>
> The Branch Council is of the opinion that every person seeking medical advice is entitled to receive it from the doctor of his choice. It is true that the most careful examination cannot provide conclusive evidence of the absence of cancer, so that no positive assurance can be given to any patient that

a malignant growth is not present. On the other hand, the most readily detectable cancers are among those which are most common. Cancers of the skin and breast alone account for some 40% of all cancers.

For these reasons, the Branch Council considers that when a patient requests a medical examination for detection of cancer, the doctor should meet the request, having first informed the patient of the limitation of such examinations and also of the possibility that further special investigations may be indicated.

PENICILLIN BY MOUTH.

THOSE who worked in hospitals when penicillin was first introduced will remember the days when patients were subjected to intramuscular injections of small doses of penicillin every three hours, day and night. Even adults found this régime wearing, and the mental trauma inflicted on the unfortunate children who had to run this gauntlet is anybody's guess. Now that penicillin is plentiful and relatively cheap and that long-acting compounds are available, it is in most cases unnecessary to give more than one or two injections per day, and we can afford to look back on earlier régimes as something out of the dark ages. The question now is, to what extent is it necessary to give penicillin injections at all? Drilled in the necessity of giving penicillin by injection, as the only route, the medical profession was initially perhaps a bit reluctant to accept the orally administrable penicillin salts when they in turn appeared. At first the idea got around that they might be used for young children with relatively minor complaints. There was a natural reluctance to abandon the demonstrable certainty of the intramuscular route for the untried oral route, by which the penicillin had to survive the vicissitudes of a bath in the gastric contents. However, it has by now been firmly established that in a wide range of conditions the appropriate penicillin salt given by mouth is just as effective as penicillin given by injection. It is over ten years since MacLachlan *et alii* published their report on a series of 149 patients with pneumococcal pneumonia, of whom the half treated with orally administered penicillin fared slightly better than the half treated by injection. Since then the introduction of phenoxymethyl penicillin (penicillin V) and other stable penicillin salts has virtually eliminated the risk of inactivation in the stomach. In spite of all this, there is still a widespread tendency for doctors to give penicillin by injection "just to be on the safe side", ignoring the remote but very real danger of an acute anaphylactic reaction. In this context, one Australian Branch of the B.M.A., in a supplement to its monthly bulletin,[2] has recently advised its members that the injection of procaine penicillin is "more dangerous, more unpleasant and no more effective than Penicillin V by mouth" and should rarely be necessary. The oral administration of penicillin does not entirely eliminate the risk of an acute anaphylactic reaction, as illustrated by a case reported in this Journal by H. Fraser,[3] but the danger of an acute reaction in such circumstances must be very much less than after an injection.

One reason for the persisting feeling of indecision as to the relative merits of orally administered and injectable penicillin is perhaps that, though the fact that adequate blood levels can be obtained by giving penicillin by mouth is well substantiated by numerous investigations, not so much has been published in the way of relevant clinical trials, particularly with reference to conditions commonly met with in general practice. For this reason we draw attention to a recent report by S. Malkin,[4] of Winnipeg, on a trial of orally administered versus injectable penicillin. Malkin specifically chose conditions commonly encountered in general practice, and his series included 7 cases of scarlet fever, 5 of severe tonsillitis, 7 of moderately severe tonsillitis, and 13 of miscellaneous infections. Sensitivity tests were carried out on the infecting organisms in all cases, and for the most part alternate patients were treated by oral and parenteral routes; only in the case of scarlet fever, 6 out of the 7 patients received their penicillin orally. Malkin used a long-acting penicillin preparation for oral administration, giving the patients of this group one tablet of "Falopen", containing 500,000 units of potassium penicillin G, twice a day; patients being treated by injection received 600,000 units of procaine penicillin G every 24 hours. Results were assessed both bacteriologically and clinically, and it was concluded that injectable penicillin did not seem to offer any therapeutic advantage in the treatment of these patients. The dosage scale appears modest, but in most cases in both series marked bacteriological improvement was noted in 48 hours, and marked clinical improvement in three days.

On the question of what is done in actual practice, we would remind readers of the results of an English survey by D. Wheatley[5] published 18 months ago. This survey was constructed from the replies to a *questionnaire* filled in by 85 practitioners in a limited area. Eighty of these doctors stated that they used oral preparations of penicillin, 66 using them for both adults and children and 14 for children only. Three-quarters of those using oral preparations stated that they found the results of oral administration comparable with those of parenteral administration, and of the quarter who considered injectable penicillin superior, eight were considered to be using the oral preparations in inadequate doses. Various oral preparations were in use, but penicillin V was that most commonly used. The most common dosage schedule employed was 60 mg. given at intervals of three to six hours for children and double that amount for adults.

These reports are but two among a number of investigations which all point in the same direction—namely, that when susceptible organisms are involved and except in cases of vital urgency, or when it is necessary to maintain particularly high levels of antibiotic activity in the blood, orally administered penicillin will do the job just as efficiently as injected penicillin.

THE CASE OF A BEST-SELLER ON RHEUMATISM.

ACCORDING to a recent annotation,[1] on November 9, 1959, the Federal Trade Commission (U.S.A.) issued an "initial decision" (to which the respondents have the right to reply) against Witkower Press, Inc. (publisher), and Dan Dale Alexander, author of "Arthritis and Common Sense". Four members of the American Rheumatism Association had testified during a long hearing. The Commission ordered the respondents, individually and through agents, to desist from offering the book for sale or distribution, and to desist from representing that it provided an adequate means (i) of treatment of the rheumatic diseases, or (ii) of arresting their progress or (iii) of relieving their symptoms. Among the Commission's conclusions are the following: "The use by the respondents of . . . false, misleading, and deceptive statements and representations has had, and now has, the capacity and tendency to mislead and deceive the purchasing public into the erroneous and mistaken belief that said representations are true and into the purchase of respondents' said book by reason thereof. The aforesaid acts and practices of the respondents are all to the prejudice and injury of the public and constitute unfair and deceptive acts within the intent and meaning of the Federal Trade Commission Act."

[1] *Canad. med. Ass. J.*, 1949, 61: 134 (August).
[2] *N.S.W. Branch B.M.A. Monthly Bull.*, February 15, 1960.
[3] MED. J. AUST., 1958, 2: 801 (December 13).
[4] *Canad. med. Ass. J.*, 1959, 81: 553 (October 1).
[5] *Brit. med. J.*, 1958, 2: 907 (October 11).
[1] *Arthritis Rheum.*, 1960, 3: 97 (February).

Abstracts from Medical Literature.

OTO-RHINO-LARYNGOLOGY.

Hyperkeratosis of the Larynx.

A. J. CRACOVANER (*A.M.A. Arch. Otolaryng.*, September, 1959) states that hyperkeratosis of the larynx is a precancerous lesion and must be treated as a potentially malignant condition. However, many of the lesions are benign, and so it is thought that radical treatment is frequently unnecessary. The problem is, how to differentiate the benign lesion from those that may become malignant and those already showing evidence of early malignancy, and how to formulate methods of managing such cases so as to eliminate the disease and at the same time avoid radical and mutilating procedures. Small localized lesions are treated by stripping the cords under direct laryngoscopy. Irritation due to alcohol, tobacco, abuse of the voice, infection, etc., must be avoided. Lesions that recur on one vocal cord or a papillomatous-appearing lesion on one vocal cord should be removed by laryngofissure. Lesions that recur on both vocal cords should be treated by radiation. If this is unsuccessful, a laryngectomy should be performed. Extensive involvement of the larynx by a warty papillomatous lesion should be treated by laryngectomy.

Corrosive Burns of the Œsophagus.

E. L. YURICH (*Laryngoscope*, February, 1959) states that early diagnosis of corrosive burns of the œsophagus is important. The history and appearance of burns about the mouth and lips, together with pain, dysphagia, and hoarseness, are indicative. With extensive burns, shock and dyspnœa due to laryngeal involvement, the diagnosis is obvious. Early (within 12 to 24 hours) œsophagoscopy under general anæsthesia is most important. Treatment consists of first neutralizing the acid or alkalis with appropriate solutions. The author does not favour the use of gastric tubes because of their possible traumatic effect. The patient is put on penicillin and steroid therapy from the first 24 hours, the latter in relatively large doses. Diet is liquid at first, then soft, and after a week solid food is given. Œsophagoscopy is repeated every 10 days until healing is complete. With this treatment eight out of 10 patients responded well. If the diagnosis has not been made within 48 hours, the steroids cannot be used. Daily dilatations then have to be resorted to. Details of late treatment are given.

Laryngocele and Laryngeal Cancer.

L. PIETRANTONI, D. FESILATI AND A. FINZI (*Ann. Otol.* (*St Louis*), March, 1959) have discussed the problem of the association between laryngeal cancer and laryngocele. Out of 857 cases of laryngeal cancer, radiological and tomographical investigation has shown the presence of laryngocele in 53 cases. A study of the specimens was possible in 31 of these cases. Macroscopic and histological studies yielded the following results: (i) The incidence of laryngocele in cases of laryngeal cancer, as shown by radiological data, reaches 6%. In view of the fact that radiological investigation often fails to reveal the existence of a ventricular herniation, the authors are inclined to believe that the real incidence is actually much higher. (ii) The ventricle was affected by the tumour in 24 out of 42 hemilarynxes examined. (iii) The presence of laryngocele is not always dependent upon the new growth; this is shown by the occurrence of monolateral tumours associated with bilateral laryngoceles, and of strictly unilateral tumours accompanied by a ventricular appendix on the same side and by a laryngocele on the opposite side. (iv) The authors consider that other factors probably play a role in the onset of laryngocele. These are, first, a predisposing anatomical factor, and secondarily, the onset of cough, dysphonia and other respiratory and phonatory alterations due to the presence of the tumour, which may cause a rise of pressure in Morgagni's ventricles.

Secretory Cysts of the Maxillary Antrum.

C. P. MILLS (*J. Laryng.*, May, 1959) discusses secretory cysts of the maxillary antrum and their relation to the development of antro-choanal polypi and suggests that these are retention or secretory cysts. He points out that there is an absence of inflammation in the histological picture of the cyst wall, which enhances his theory. In most cases there has been a history of previous antral infection which leads to an œdematous mucosa. Ducts of large acinous mucous glands become blocked and form retention cysts, some of which rupture submucosally to form a few larger cysts, the mucosa of which continues to secrete. They enlarge, pushing the mucosa of the antrum away from the bony wall, till finally one large extramucosal cyst is formed. The biochemistry of the fluid is discussed. The author also suggests that antro-choanal polypi are really cysts extruded via the natural antral ostium. Sometimes antral lavage will empty a cyst, the wall of which does not re-form, and no further symptoms arise. In others, removal via the sublabial approach, leaving the remainder of the antral mucosa intact, is suggested.

Pathology of Fœtal Ears after Maternal Rubella.

G. KELEMEN AND B. N. GOTLIB (*Laryngoscope* (*St Louis*), April, 1959) point out that while there is ample clinical evidence of deafness in children born after the mother has had rubella in the first trimester of pregnancy, the actual pathological lesion in these cases is not clear. The authors report on material from four cases in which pregnancy was interrupted between the tenth and the eighteenth weeks. The indication for surgical interference, hysterotomy in three cases and curettage in one, was rubella of the mother in early pregnancy. Both temporal bones were examined in serial sections in the cases in which hysterotomy was performed; a fragment from the specimen obtained by curette was similarly examined. Sporadic lesions were found. These were: a massive hæmorrhage in vestibular scala, some blood mixed in the mesenchyme of the perilymph, band fixation of the tectorial membrane to the membrane of Reissner. However, the specimens failed to show any aural histo-pathological lesions which could be regarded as definitely responsible for the hearing loss in the progeny which frequently follows maternal rubella. The authors suggest that the most promising clue may be vascular fragility, leading eventually to abnormalities. In the central as in the peripheral hearing organ, vascular damage may become a factor at periods of strain, such as during gestation, at delivery, or at any point of peri-natal or post-natal life. Study of viral effects on blood vessels may give a clue to a pathological basis for deafness as part of rubella embryopathy. The authors point out that their material, obtained by surgical intervention and fixed immediately, should not have undergone any post-mortem changes. Also, the material was uniform in that the mothers belonged to the same age group and developed rubella at approximately the same stage of gestation.

The Mandibular Joint Syndrome.

J. B. COSTEN (*Laryngoscope* (*St Louis*), April, 1959) states that identification of the mandibular joint syndrome involves sorting out its qualities from the maze of known reactions of fifth nerve pain. Otalgia, vertex pain, glossodynia, and varieties of trismus which activate the mechanism, are clearly established in diagnosis of this symptom complex. Once the painful reflexes are established, there is a reflex contraction of the masseter group of muscles which perpetuates the trismus cycle with further pressure on the sensory nerve area. The author classifies the syndrome according to whether it is (i) temporary, with otalgia, trismus and subjective deafness due to overclosure of the jaws leading to compression of the Eustachian tubes; (ii) semi-permanent, with pain effects and structural changes; (iii) semi-permanent, recurrent, with or without pathological changes in the joint; (iv) permanent, with resulting ankylosis. He states that, as regards treatment, it is extremely important to apply direct measures to the joint action, such as elastic splinting of the jaw and injection of steroid substances. These should be used routinely, over long periods, even in the presence of suspected neurosis. It is better to splint for repeated short periods rather than for prolonged uninterrupted periods. The type of splinting required is illustrated. In cases in the permanent group some form of surgical operation on the joint will probably be necessary. Amputation of the condyle may be performed, with resection of all fibrous scarring about the joint and coronoid process.

Experimentally Induced Ankylosis of the Stapes.

R. J. BELLUCCI AND D. WOLFF (*Laryngoscope* (*St Louis*), March, 1959) point out that, if experimental ankylosis could be induced, one step further in research on otosclerosis might be accomplished. They have met with some success in this work by the use of one of several methods. These include electrocoagulation and mechanical trauma in experiments with cats, and the feeding of excessive doses of lathyrus factor in rats. The authors state that

evidence is accumulating that altered nutrition may cause ankylosis of the stapedio-vestibular joint, but that the interpretation of their findings will require the investigative skill of a chemist and a biochemist. It is not known whether the perivascular lesion in the bone is due to an electrochemical effect or merely a thermal effect. There may be a true electrolysis of the bone. If so, the authors ask, what human pathological condition induces this kind of reaction in cases of otosclerosis? They state that the potential lability of bone has been clearly demonstrated before, but they ask what chemical change in the tissue fluid is able to wash out the bone salt so completely and yet so locally.

OPHTHALMOLOGY.

Hormone Treatment of Herpes Zoster Ophthalmicus.

H. SCHEIE AND T. MCLELLAN (*A.M.A. Arch. Ophthal.*, October, 1959) present their observations on the use of corticotropin and corticosteroids in the treatment of herpes zoster ophthalmicus. They base their observations on the treatment of 36 patients. The ocular involvement may include iridocyclitis, scleritis, secondary glaucoma and corneal opacity. Less common complications are optic atrophy, retinal detachment and extraocular pareses. All patients were treated by the topical application of atropine and hydrocortisone-neomycin ointment. Forty units of corticotropin were first given intravenously, then further doses were given intramuscularly, and then corticosteroids were given orally. Pain responded promptly. The aqueous began to clear by the second to the fourth day. Secondary glaucoma was also favourably influenced.

Treatment of Ophthalmic Herpes Zoster with Protamide.

G. S. SFORZOLINI (*A.M.A. Arch. Ophthal.*, September, 1959) reports on the use of protamide in 42 patients with herpes zoster ophthalmicus. There was a favourable response in nine-tenths of the patients. Protamide is a proteolytic enzyme prepared from hog stomach made up as an injectable sterile colloidal solution. Protamide 1·3 ml. was injected daily for three consecutive days and thereafter at intervals of one or more days until pain and lesions had disappeared. Local therapy, that is, mydriatics and cortisone, was used concurrently. The author believes that protamide gives more satisfactory results than antibiotics, vitamins or the corticosteroids.

Hypophysectomy for Proliferative Diabetic Retinopathy.

S. VANNAS *et alii* (*A.M.A. Arch. Ophthal.*, September, 1959) report on 10 diabetic patients who were subjected to hypophysectomy. There were four women and six men; their diabetes was of a labile type and had lasted for from 10 to 18 years. Nine patients had diabetic retinopathy; the tenth patient had severe nephropathy. Nine of the patients were alive at periods of three to 34 months after operation. In seven patients the vision of the better eye remained unchanged or improved a little. It deteriorated in the other three. There was improvement in the fundus appearance in all cases with disappearance of microaneurysms and new formed vessels. Hæmorrhages were absorbed. Waxy exudates and cotton-wool patches also tended to disappear and the rate of proliferation diminished.

Lens Surgery in Marfan's Syndrome.

D. KRAVITZ (*A.M.A. Arch. Ophthal.*, November, 1959) makes a plea for operation in Marfan's syndrome when the lens is dislocated in such a manner as to interfere with vision to the extent of retarding the child's development. He reports on four patients on whom he operated; vision improved in all patients. His technique was to fix the lens with a Ziegler needle and then to do a discission with a generous capsulotomy with a second needle. He believes that the risks of glaucoma and detachment are not increased by operating in these cases. A high percentage of patients on whom operation is not performed develop such complications.

Biomicroscopic Examination of the Fundus.

E. ROSEN (*Amer. J. Ophthal.*, December, 1959) discusses the use of a plus 55 lens in fundus examination. The method is a form of indirect ophthalmoscopy using a slit beam and binocular microscope. The patient should be comfortably seated with chin and head immobilized. To see the fundus clearly the distance between the patient's eye and the microscope should be increased three or four inches. A plus 55 or plus 60 lens is held in front of the eye. This lens is most readily obtained from the proximal portion of an eyepiece of an ordinary microscope. A moderately thin beam of light should be used, together with the longest beam length. A field six times the diameter of the disc may be obtained, whereas with the Hruby lens the visible field is about one disc diameter. Once the disc comes into focus the "joy stick" should be locked. The entire fundus, including periphery, can be examined by various movements of the lens. Much weaker illumination is required than with the Hruby lens.

Lamellar Keratoplasty.

D. PIERSE AND T. A. CASEY (*Brit. J. Ophthal.*, December, 1959) report on 48 cases in which lamellar keratoplasty was performed. About one-third of these operations were undertaken as an out-patient procedure. Most of the other patients were in hospital for a short time only. Some operations were performed for pterygium, in which case a rectangular graft was usually employed, half the thickness of the cornea in depth and extending on to the sclera for 2 mm. Therapeutic grafting was employed for active keratitis, especially herpetic keratitis, in all cases which had persisted for two months. The procedure proved successful with recurrent rosacea keratitis and with herpetic keratitis. As a means of improving vision and to prepare a markedly vascularized cornea for further grafting, the procedure was invaluable. The authors used a rectangular graft and fixed the graft with a suture which combined the direct and overlay sutures.

Ocular Signs and Symptoms in Myasthenia Gravis.

N. S. SCHLEZENGER AND W. A. FAIRFAX (*A.M.A. Arch. Ophthal.*, December, 1959) surveyed 52 patients with myasthenia gravis. The age incidence varied from 18 months to 75 years, with peak incidence in the third to fifth decades. There is a congenital form of myasthenia gravis with onset at birth and characterized by bilateral ophthalmoplegia. The disease tends to effect females in the younger age groups and males in the older age groups. The initial symptoms are often extraocular muscle paresis and ptosis. There may be complete extraocular ophthalmoplegia. The authors' series supports the concept that myasthenia which is still limited to the eyes after two or three years will remain purely ocular. Of 20 patients in whom myasthenia became generalized, 17 were so affected in the first year, two in the second year, and only one in the third year. Neostigmine or "Mestinon" proved to be satisfactory in controlling symptoms. ACTH in a total dose of 600 mg. given in doses of 20 mg., is effective in reducing or eliminating extraocular muscle paresis. The duration of partial or complete remission has varied from three to 12 months.

Tonometry With and Without a Recording Galvanometer.

W. ROBERTS (*Amer. J. Ophthal.*, January, 1960) considers tonometry an essential aid to diagnosis in early glaucoma, to classification in equivocal cases, to evaluation of the efficiency of therapy in simple glaucoma, and as an aid in the determination of the type of surgery needed in angle-closure glaucoma. He discusses the performance of tonometry with and without a recording galvanometer, in the light of 790 tonometric estimations. Simultaneous galvanometer recordings and direct readings taken from the tonometer at half minute intervals were made in all instances. A comparison of the two methods revealed unsatisfactory correlation between the two techniques, with an excessive number of large deviations. The author considers that the direct reading technique is an unsatisfactory substitute for the standard technique of tonography.

The Effect of Demecarium Bromide on Intraocular Pressure.

S. M. DRANCE (*A.M.A. Arch. Ophthal.*, October, 1959) has studied the effect of demecarium bromide on normal and glaucomatous eyes. In normal eyes, 0·25% and 0·1% demecarium bromide solution produced a fall in intraocular pressure. Side effects were vasodilatation, blurring of vision and headache. Glaucomatous subjects were treated with solutions of 0·5%, 0·25% and 0·1% demecarium bromide. Out of 40 eyes treated, 38 showed a satisfactory drop in pressure. The side effects were the same as experienced in non-glaucomatous eyes, but these tend to wear off with continuous use of the drops.

British Medical Association.

VICTORIAN BRANCH: SECTION FOR THE STUDY OF ALLERGIC DISEASES.

A MEETING of the Section for the Study of Allergic Diseases of the British Medical Association (Victorian Branch) was held on August 6, 1959, at the Medical Society Hall.

Serum Sensitivity Testing.

DR. JOHN C. TRINCA read a paper entitled "Recent Developments in Serum Sensitivity Testing" (see page 913).

DR. G. C. T. BURNS inquired whether test doses were to be included with tetanus antiserum in the future.

DR. C. SUTHERLAND considered that skin tests for serum sensitivity were, in general, unreliable. He said that he considered a small (No. 26) needle essential in carrying out the tests.

DR. E. WHITE stressed the fact that an occasional intradermal test might literally be intravenous and this could give a general reaction. He thought that delayed reactions from a test dose occurred up to two hours after administration of the dose.

DR. S. BRAND advised a scratch test initially with the diluted serum, rather than a subcutaneous dose.

DR. S. WIENER thought that in some cases of intradermal testing with negative results the dose might have been given subcutaneously.

DR. E. CHENOWETH said he believed all asthmatics should be actively immunized against tetanus.

DR. M. WILSON asked whether it was possible to immunize passively a patient during the refractory phase, after a general reaction.

DR. V. G. BRISTOW said that he thought untrained observation of test doses was unreliable. He advised the use of antihistaminics during desensitization to tetanus antiserum.

DR. P. WARD FARMER mentioned intrinsic sensitivity to horse serum. He considered the scratch test very important and inquired whether a smaller test dose than 0·5 ml. diluted one in 50 and given subcutaneously, should be used. He also asked whether animal sera other than horse serum could be used in the manufacture of tetanus antiserum.

Medical Societies.

PÆDIATRIC SOCIETY OF VICTORIA.

A MEETING of the Pædiatric Society of Victoria was held on July 8, 1959, at the Royal Children's Hospital, Melbourne.

Adreno-Genital Syndrome with Unusual Features.

DR. M. ROBINSON discussed the case of a child who presented at the Royal Children's Hospital at the age of four weeks with a history of vomiting, failure to gain in weight and failure to maintain hydration since birth. Initial investigations failed to elicit a cause for the symptoms, but the electrolyte pattern suggested an adrenal salt-losing state. Treatment with cortisone acetate, desoxycorticosterone acetate and additional salt controlled the infant's symptoms and thus supported the diagnosis. From birth this infant had been regarded as male and had been circumcised; however, testes were not palpable in the scrotum. After some weeks, when the infant was thriving, further investigations were performed. The twenty-four hour excretion of 17 ketosteroids was 6·4 mg., which was diagnostic of congenital adrenal hyperplasia. Skin biopsy did not help in determining the sex and laparotomy was performed. This showed a normal uterus, ovaries and Fallopian tubes. Thus the patient was a female with congenital adrenal hyperplasia, with a completely masculine external genital appearance except for the absence of testes. This was only the eighth recorded case of such an extreme degree of masculinization of the female in congenital adrenal hyperplasia, and the third to be diagnosed during life. It was the first to be diagnosed before the age of twelve months.

Dr. Robinson said that after much discussion, it had been decided to raise the infant as female. The main factors weighing against success when the true sex was contradicted by the external genital appearances were the genital anomaly, hirsutism and the family influence. With regard to the genital anomaly, the urethra passed directly through the clitoris to open at the tip of the glans, and the labia were fused and and corrugated to resemble a scrotum. Despite that, Mr. Wakefield had been able to make the external genitalia appear normally female. Hirsutism had persisted despite normal 17-ketosteroid excretion, normal growth and near-normal bone age. That remained the big problem and was under investigation. The third problem was that of the family attitudes; the parents, and in particular the grandparents, had been very confused and somewhat hostile, although they readily agreed to raise the child as a female. They were receiving psychiatric help. It was most important that the family thoroughly understood the problem and accepted the child as female; unless that was achieved, gross problems would arise.

Operation had been performed by Mr. Wakefield, and a very successful result obtained. After the operation a severe Addisonian crisis had developed. Dr. Robinson said that the case was again unusual in that it had been generally accepted that the salt-losing tendency which occurred in one-third of such cases disappeared by the age of two years. Recently a salt-losing hormone had been discovered, and he hoped to follow up that facet.

MR. A. WAKEFIELD discussed the technicalities of the surgery involved in altering the external genitalia to resemble as closely as possible, those of the female. He pointed out that merely to amputate the phallus at its base would not achieve that result in the case under discussion, and that it was necessary to approach the problem from four points of view: (i) the conversion of the scrotum into a vulva by separating its two halves to resemble labia and lining the groove between with new skin from elsewhere; (ii) the transfer of the urethra into the floor of that vulva in approximately the normal situation; (iii) the conversion of the existing phallus into something which resembled a clitoris in both structure and position; (iv) the establishment of a vagina in continuity with the uterus.

Mr. Wakefield said that the first three of those objectives had so far been achieved, and indicated the methods by which that had been carried out. He pointed out the difficulties of establishing an adequate vagina at that stage, and said that it was the intention to leave it until the child was aged abou ten years or even a little later. Finally, Mr. Wakeeld indicated the importance of planning the surgery carefully to reduce the number of operations to a minimum because of the hazards of those procedures. He said that, notwithstanding all those difficulties in the case under discussion there seemed no reason why one should aim at anything less than an adult woman capable of sexual intercourse and reproduction.

Children Affected by Heat-Wave Conditions.

DR. D. DANKS discussed the large group of infants and children seen at the Royal Children's Hospital in January, 1959, suffering from illness principally due to heat-wave conditions. He said that the information on which his paper was based had been collected by Dr. Daryl Webb, Miss Jean Allan (who had visited the homes from which most of the patients came) and himself. In January and early February, 1959, there had been three periods of century heat in Melbourne, the first of which had lasted nearly four days, with shade temperatures above 107° F. (41·7° C.) on three of them and a low relative humidity. The two latter periods were shorter, slightly less severe and more humid. All the cases occurred in the first period, when 47 patients presented; six were dead on arrival, and six others died after admission to hospital. The figures included only those cases in which the heat was considered the only, or at least the outstanding, cause of illness. In all admissions over that period heat played some part; for example, patients with acute appendicitis required intravenous therapy and cooling. The heat wave was Melbourne's worst for 50 years, and the hospital records did not show any previous group of cases of comparable number. The medical literature contained no strictly comparable group. The greatest rush of admissions occurred on the afternoon and evening of Sunday, January 18 (the second hot day), and in the early hours of the next morning; 23 patients presented. Three of these were dead on arrival, and two others died within an hour. Under the circumstances, few laboratory investi-

gations were possible and records were scanty. On January 19, facilities were better organized to cope with the 14 patients presenting (two more dead on arrival); five patients presented on January 20, one dead on arrival.

When the causes were analysed, the first striking feature was that nearly half the children (22) were aged between three and nine months. In view of the rather poor homœostatic mechanisms of the small infant, one would not have expected that relative sparing of those aged under three months (only three cases). Two factors might be important; firstly, it had been shown that newborn babies could not sweat, and that that ability might not develop for several weeks; secondly, older infants having educational diet refused fluids more often than younger ones. It was also noted that those young infants who presented did so earlier than older ones—nearly all those aged under six months were admitted to hospital on the first two days. The sex distribution was equal among the infants, but very unequal in children aged over one year (15 males, three females). Although adult males are known to sweat more than females, that fact was rather inexplicable. Mortality was even through all age groups and between the sexes.

Dr. Danks went on to say that most patients presented very similar clinical pictures. Features were extreme dehydration with cyanosed extremities but relatively strong pulses, severe impairment of consciousness and hyperpyrexia with dry skin. In contrast to overseas experience, there was no case of hyperpyrexia without dehydration; that was probably related to the low humidity. A number of patients seemed moribund. Only five had had convulsions prior to their admission to hospital. The severity of all the major features had a marked bearing on mortality. The history revealed that the final decline to that parlous state had been abrupt in most cases. Unfortunately serum electrolyte estimation had been performed in only a few cases; but all patients with the clinical pattern described showed elevated levels—hypertonic dehydration. That would be expected, as skin and respiratory fluid loss was hypotonic. A small group of patients from the country, who had been exposed to severe heat for a week or more, was seen. Clinically and biochemically they too showed features of hypotonic dehydration.

Dr. Danks said that when one came to a consideration of the factors which caused those 47 patients to be more severely affected by the heat than were others in the community, several factors stood out. Refusal of ordinary fluids and food was present in 37 cases, and for more than two days in 22 of them. Failure to offer the child extra watery fluid when the heat began was alarmingly common (23 cases), and some were never offered anything other than their usual milk (11 cases). Vomiting was a marked feature in nearly half the cases (20), though in some it occurred only in the last 12 hours. Diarrhœa occurred in 11 cases, but was severe in only four. Respiratory infections played a part in some cases (12) and teething in others (six). Feeding difficulties had existed before the heat wave in 14 cases. Surprisingly, very few children had been overclad, and most mothers had attempted to cool their children. Although all those factors must have contributed to the illness, they did not influence its severity or mortality. In contrast, the presence of underlying chronic disease did influence both incidence and outcome; underlying diseases included mental retardation (eight severe cases), fibrocystic disease of the pancreas (two cases), diabetes (one case) and various disorders (four cases). A disturbing factor was that almost half (13 of 31) of those parents who called a doctor received either unduly delayed or rather ill-directed advice; a number of those cases had a fatal outcome. Similarly, those parents who asked for advice at health centres were not greatly helped.

The homes and mothers of 38 of the patients were assessed by Miss Allan. She considered that the distribution of standard and substandard homes and the standard of maternal care were fairly average, but noted that three of the children who were dead on arrival came from extremely bad homes and two had very dull mothers. Miss Allan had made a special assessment of the heat of that part of the house where the patient had been kept, and had found that in 21 cases it was exceptionally hot (for example, in low-roofed fibrous plaster or iron houses). All the children dead on arrival came from such homes.

On the patients' arrival in hospital, treatment had consisted of giving them fluid and cooling them. In almost all cases fluid had been needed intravenously, and needed urgently—many infusions were begun in the casualty department or after the child had been rushed to the ward, and in some cases the femoral vein had had to be used because vasospasm in the saphenous vein had obstructed the flow line. The fluid used initially varied in different units from one-eighth normal saline to one-half normal saline. Analysis of the results failed to show any advantage gained from the use of any one fluid or from any particular rate of administration. Cooling had been with spirit or ice packs with the use of fans, and had been generally effective. That initial treatment had produced in most cases a gratifying and rapid improvement in the circulation and level of consciousness. In many cases a new worry had quickly developed in the form of convulsions, which lasted for many hours in some cases and were associated wiht a raised mortality. In cases of hypertonic dehydration the event of late convulsions was common, and was sometimes attributed to over-rapid rehydration, with water intoxication; that could not be proved in those cases.

Study of the six patients dead on arrival revealed that four had had to come considerable distances to the hospital; when one remembered how near to death on arrival several of the survivors were, that became of great importance. It was difficult to assess the significance of the presence of definite but early pulmonary infective changes in four cases. Careful consideration of those who died in hospital again revealed difficulty in reaching the hospital in the two cases in which death occurred very soon after the patients' admission to hospital. In two other cases, treatment was probably at fault—too little salt had been given to a child with fibrocystic disease of the pancreas, and insulin-induced hypoglycæmia occurred in one child who showed hyperglycæmia. Underlying disease was present in the remaining two—cerebral agenesis in one, severe gastro-enteritis in the other.

Dr. Danks then said that those experiences allowed one to formulate certain recommendations in an attempt to prevent a recurrence of such a disaster. Most important was the education of mothers (and health centre sisters and doctors) to realize that in hot weather every baby and child needed extra water. Water, not milk, should be given, and salt should not be added unless heat had been sustained for many days. Publicity for those facts at the beginning of hot spells would be wise, and might be effective in preventing cases in later heat waves. Treatment of patients along the lines indicated seemed reasonable, although, once an adequate circulation had been established, caution about the rate of intravenous administration of fluids was needed. However, the extreme urgency of commencing intravenous therapy had to be appreciated. There might be a case for the administration of antibiotics to control chest infection. Convulsions had to be quickly controlled, and perhaps hypothermia was the best measure auxiliary to sedatives.

In conclusion, Dr. Danks said that the review of 47 children ill as the result of the January, 1959, heat wave showed that the low humidity had been an important factor, and that hypertonic dehydration was the outstanding clinical feature; that failure of mothers to offer extra water early in the heat wave had been probably the most important causative factor, though minor acute illnesses and underlying chronic diseases played a part in some cases; that convulsions during rehydration had been frequent, severe and dangerous, but had not been relatable to either rate or type of intravenous therapy; and that the distance travelled to the hospital had been an important factor in causing deaths before or shortly after arrival.

DR. D. RANKIN said that, during January and February, 1959, several reports had reached the State Department of Health attributing large numbers of deaths to the heat-wave conditions which existed in those two months. Also, the Commonwealth Statistician's Office in Melbourne had reported that 145 death certificates had been received on which excessive heat or related conditions had been given as a contributory cause of death. The number of deaths in which the sole cause had been given as excessive heat, and therefore registered as such, was not yet known, but indications were that it would be greatly in excess of that in previous years. In 1955 there had been none, in 1956 and 1957 there had been one in each, and the figure for 1958, although not yet known with certainty, had also been very low.

During January and February there had been two periods of excessive heat; the first was from January 9 to 25, a period of 17 days in all, during which time the daily maximum temperature had fallen below 80° F. on only two days. Most deaths had been associated with the first period. Similarly, most of the terminal illnesses had commenced in that period.

That picture of deaths associated with extreme climatic conditions was seen even more clearly if one took into account the maximum daily effective temperature. The effective temperature was one which took into account the dry-bulb and wet-bulb temperatures and the air movement, and so was really a more accurate representation of climatic conditions than was the dry-bulb temperature alone. The mean maximum daily effective temperature for the period 1950 to 1959 for the two months under consideration was 72° F. That had been exceeded from January 9 to 25, with only two days in which the maximum effective temperature had fallen below that value.

The increase in deaths attributable to heat in the first period might be due to two main factors. Firstly, certifying medical practitioners might, by the time the temperature had reached its first peak (January 17 to 20), have become more aware of the heat themselves, and so have been more likely to attribute the deaths of others to it—the diagnosis of the cause of death might have been influenced by the doctors' own discomfort. Secondly, the period of heat preceding the peak of January 17 to 20 might have so exhausted the susceptibles in the population that the peak of temperature killed them—the deaths had really been due to heat. That second factor might well account for the fact that in the period of excessive heat which followed there had been comparatively few deaths attributed to heat.

Dr. Rankin said that it was of interest to note that if one plotted the number of terminal illnesses which had commenced on each day against the maximum daily temperature (and the maximum daily effective temperature), there seemed to be some relationship between the first period of great heat and the onset of an appreciable number of fatal illnesses. Twelve deaths occurred in children aged under 10 years; the highest incidence occurred between the ages of 70 and 89 years, in which age group there had been 84 deaths. Of the total of 145 deaths, 51 occurred in males and 94 in females. Fifty-six deaths occurred in institutions and 89 out of institutions.

DR. V. COLLINS said he wished to emphasize the great importance of offering infants extra fluid other than milk during heat-wave conditions. Knowledge of that important principle should be as widely disseminated as possible.

MEDICAL DEFENCE SOCIETY OF QUEENSLAND.

ANNUAL MEETING.

THE fifty-eighth annual meeting of the Medical Defence Society of Queensland was held at B.M.A. House, 88 L'Estrange Terrace, Kelvin Grove, Brisbane, on Tuesday, April 12, 1960, Dr. F. W. R. Lukin in the chair.

Annual Report.

The annual report for the year ended December 31, 1959, was adopted. The report is as follows:

The Council of the Medical Defence Society of Queensland has pleasure in presenting the fifty-eighth annual report for the year ended December 31, 1959.

Membership.

The membership of the Society is now 971 as against 941 last year. During the year 105 new members were elected and four returned from overseas. Our losses were as follows: left the State 47, resignations 7, deceased 8, lapsed by arrears 17.

There are 17 members who have indemnity insurance cover with other approved organizations.

Obituary.

We regret to record the deaths of the following members: Dr. K. J. Hill, Dr. A. J. Reye, Dr. J. Hedley Brown, Dr. C. Shellshear, Dr. J. Pietsch, Dr. G. C. H. Hogg, Dr. Max Berg and Dr. J. R. S. Lahz.

Office Bearers and Council, 1959.

The following office bearers were elected by the Council: *President*, Dr. F. W. R. Lukin; *Vice-President*, Dr. Athol Quayle; *Honorary Treasurer*, Dr. T. V. Stubbs Brown; *Honorary Secretary*, Dr. D. R. L. Hart; *Councillors for 1959*: Dr. B. N. Adsett, Dr. T. R. Biggs, Dr. H. W. Horn, Dr. N. W. Martin, Dr. Robert Miller, Dr. W. J. Saxon, Dr. J. G. Wagner.

The following Councillors who retired in conformity with the Articles, were unanimously reelected: Dr. T. V. Stubbs Brown, Dr. W. J. Saxon and Dr. J. G. Wagner.

Medico-Legal.

During the year twelve cases were submitted to the Society for advice or action, and six were carried over from the previous year. All were dealt with to the satisfaction of the Society and of the members concerned. Writs have been issued in two cases carried over from last year, and in one case submitted this year which the Society is defending. Other matters on which members sought advice were dealt with by the Council or the Secretariat.

General.

During the year, advice was received from the Medical Protection Society of London that a member would no longer be required to pay a final compound subscription on retirement, in order to remain indemnified for previous years. If, however, he wished to be covered for any casual attendances for accidents or emergencies, then a final compound subscription would be necessary.

In accordance with Council's policy, a further £800 of Commonwealth Inscribed Stock, which matured in 1959, was used to invest sums of £500 in both the Southern Electricity Authority and the State Electricity Authority Loans bearing interest at 5½%.

Finance.

It will be shown by the balance sheet that the net surplus for the year ended December 31, 1959, amounted to £650 14s.

Some items of income and expenditure are as follows:

Receipts:	£	s.	d.
Annual Subscriptions Medical Defence Society of Queensland	538	2	6
Entrance Fees	99	15	0
Subscriptions, Indemnity Insurance, Medical Protection Society Ltd., London	6,770	11	5
Interest—			
Commonwealth Government Inscribed Stock, City Loan and Southern Electricity Inscribed Stock	424	10	4
Commonwealth Savings Bank	2	5	1
National Bank of Australasia	49	15	2

Expenditure:	£	s.	d.
Amount remitted to Medical Protection Society	4,909	17	6
Secretarial and Clerical Assistance	350	3	4
Postages, Duty Stamps, Printing and Stationery and Sundries	48	19	6
Audit Fee	18	18	0
Legal Expenses	8	18	6
Federal Income Tax for year ended December 31, 1958	35	4	0

The total assets of the Society amount to £14,807 16s. 1d., which include the following cash balances:

	£	s.	d.
National Bank of Australasia Ltd.	3,932	4	2
Petty Cash	3	6	1

The Society's investments total £10,822 18s. 10d., comprising £8322 18s. 10d. in Government Inscribed Stock, £1500 in Brisbane City Council Inscribed Stock, £500 in Southern Electric Authority Inscribed Stock and £500 in State Electricity Authority Inscribed Stock.

Balance Sheet and Financial Statement.

The balance sheet and financial statement for the year ended December 31, 1959, was adopted.

Election of Councillors.

The following Councillors, who had retired in conformity with the Articles of the Society, were unanimously reelected: Dr. T. R. Biggs, Dr. H. W. Horn, Dr. Athol Quayle.

Election of Auditors.

Messrs. Groom, Sanderson and Company, Chartered Accountants (Australia), were reelected auditors for the ensuing year.

Out of the Past.

BUBONIC PLAGUE.[1]

[From the *Australasian Medical Gazette*, November, 1900].

THE plague is not yet quite extinct in Queensland, though few cases are now coming to light. Up to October 27th the total number of cases was 129. Of these 55 died, 72 recovered and were discharged, and 2 remained under treatment. The cases occurred in the following districts: Brisbane 50, Townsville 37, Rockhampton 35, Cairns 5, Ipswich 1, Charters Towers 1, No cases occurred among contacts who were isolated.

Correspondence.

AN APPEAL FOR MICROSCOPES.

SIR: May I again through your columns appeal to doctors who have no further need of their microscopes to give them to the Christian Medical College and Hospital, Vellore, South India?

The Vellore Christian Medical College and Hospital is a medical training centre affiliated with Madras University, and in addition to treating 180,000 out-patients per year, has 800 beds for in-patients. It has 300 students studying for the M.B., B.S. degree, as well as about 20 post-graduates working for the M.D. or M.S. degrees. Microscopes are urgently needed for the teaching programme.

Australian doctors who have no further need for microscopes which they may have bought as medical students may be willing to give them to Vellore. The College and Hospital has international and interdenominational backing from 40 churches and missions throughout the world, and is worthy of support.

I will be personally responsible for collecting the microscopes and shipping them to Vellore.

Yours, etc.,
R. L. WALKER,
Honorary Secretary.

Australian Board of the Vellore
Christian Medical College,
193 Macquarie Street,
Sydney.
May 26, 1960.

SURGERY AND THE GENERAL PRACTITIONER AND PROFESSIONAL UNITY.

SIR: It is heartening to see that the spirit of our fathers is stirring in the profession—many of us feared it was extinct.

Some excellent correspondence in THE MEDICAL JOURNAL OF AUSTRALIA on pharmaceutical benefits was topped off in the issue of May 14 by some first-class replies by Dr. Long, Dr. McDonald and Dr. Cambourn to the article in the *Australian Women's Weekly* written by a self-styled surgeon—anonymously.

Dr. Long and Dr. McDonald have put the matter so clearly that I have little to add; but it would be a good thing in the interests of both the profession and the public if their letters were reprinted in the Journal and copies sent to the *Australian Women's Weekly*.

Let us be practical and face facts. Visualize, if you can, the patient with a ruptured ectopic, anxiously waiting in a country hospital for our anonymous friend to rush up 200 miles (or even 40 miles) to operate on her; I am certain she would prefer (and rightly so, too) her lowly general practitioner to hop in and stop the bleeding, without wasting valuable time just to give her the opportunity of having a post-mortem done by a "highly trained specialist".

A bit of experience in country practice could well be of tremendous value to the aspirant to specialization, not to mention the understanding it would give him of the problems and responsibilities faced by the country general practitioner.

It would be, of course, foolish for general practitioners in general to arise in arms against the Royal Australasian College of Surgeons because of the braying of one rat-bag. Nevertheless, the danger of a rift in the profession must not be underestimated. In this country there is much good sound surgery done by general practitioners, particularly in coping with emergencies—and, of course, some mediocre work. Likewise many of our specialist surgeons are in world class and most are sound; but, too, there are some whose work and principles are equally bad. If the writer of the article in the *Australian Women's Weekly* is so hard up that he had to descend to that sort of rubbish to earn a crust, perhaps he is of the last classification.

Suffice it to say that the public and the profession (surgeons included) have been done a great disservice by this affair. Dr. Cambourn's suggestion that the anonymous untrained surgeon should let us know his identity through this Journal is a good one; but it will not bear fruit, because, obviously, like the skeleton at the Medical School, he "hasn't got the guts".

Yours, etc.,
D. L. GRAHAM.

Meehan Street,
Yass,
New South Wales.
May 16, 1960.

RESTLESS LEGS.

SIR: Under "Current Comment" in the Journal of May 7, I was most interested to read about "Restless Legs". As you say, this is a very distressing complaint, and those that have described it have probably been sufferers as I have since I have had poliomyelitis. It would seem to be definitely associated with fatigue, and as Ask-Upmark said, it is definitely relieved by lying in the prone position.

Yours, etc.,
A. M. MACINTOSH.

Caringbah Chambers,
Cnr. Port Hacking Road and Mansfield Avenue,
Caringbah, N.S.W.
Undated.

ALCOHOL AS A FACTOR IN VICTORIAN ROAD COLLISIONS.

SIR: I read with great interest Dr. Birrell's paper on alcohol as a factor in road collisions (MED. J. AUST., May 7, 1960, page 713) and your own interesting comments in the editorial of the same issue. There is nobody more qualified than Dr. Birrell to present figures on the relation between alcoholic intoxication and road accidents; but Dr. Birrell admits himself that his figures are not based on a full scientific method of investigation, and he calls for a research body to deal more in detail with the problem concerned. May I join with him in his plea, by pointing out that the same difficulties, if not greater ones, apply when one attempts to correlate personality disorders with driving conditions.

In my study of this problem (MED. J. AUST., August 30, 1958, page 282) I suggested the establishment of a drivers' guidance council, which would serve both the purpose of assisting accident-prone drivers in their problems and of compiling scientific data. In view of the importance of the problem, it is felt that the time has come when both problems, the one of the alcoholic driver and the one of the psychologically disturbed driver, should be taken up jointly and dealt with quickly if human life is to be saved.

Full credit is given to the importance of alcohol in road accidents, and to the reliability of blood tests and to the necessity of introducing legislation making them compulsory. With all respect to the frequency of alcoholic intoxication as the cause of road accidents, we should not underestimate the significance of other factors. Firstly, there are more neurotics than alcoholics in the community, and unfortunately there are in some communities more psychopaths than neurotics. Secondly, there are many people who drive "downtown" in a state of temporary neurotic reaction caused by factors such as unhappy marriage, financial worry, court proceedings or sickness in the family. It may be they are going to face a difficulty or even an ordeal in the next hours of the day, and they are not mature enough to brace themselves against the nervous reaction affecting driving. Thirdly, we have a great number of people who are sick themselves and who get easily tired, who take drugs and so on, and

[1] From the original in the Mitchell Library, Sydney.

finally there are alcoholics who are not under the influence while driving. They may, however, appear to be under influence because of permanently slurred speech, staggering and slowing down of psychomotor responses. These people will not show alcohol in their blood while they are not drinking.

It is, therefore, important—as you say in your editorial, Sir—that besides punishing the responsible, when the damage has been done, one should also take care that these accidents should never happen. One should, therefore, take care of neurotics, psychopaths, sick people, and alcoholics who do not drink at the time of driving. That means prevention and treatment by psychological means. Let us have assistance from the Government, either State or Federal, for scientific research into psychological aspects of driving and into psychological aspects of alcoholism. We may then save human life, losses in industrial capacity and misery to families.

Yours, etc.,

I. A. LISTWAN.

193 Macquarie Street,
Sydney.
May 27, 1960.

HYDATID DISEASE IN A CHILDREN'S HOSPITAL.

SIR: I have read with great interest Dr. N. A. Myers' paper "Hydatid Disease in a Children's Hospital" (MED. J. AUST., May 21, 1960), and commend his industry in compiling this record covering a period of some 22 years. Although the number of cases seen during that time (72) may seem small in comparison with other infections and therefore less worthy of public health notice, the author is right in urging more active steps to reduce this avoidable hazard of childhood.

He is wrong, however, in including Iceland in his quintet of high-incidence regions, since that island no longer lays claim to such distiction, and indeed is cited as a shining example of hydatid reduction. Where once it was estimated that one person in seven carried a cyst, the disease has become a rarity only seen in the bodies of very old people on the autopsy table. An account of the history of echinococcosis in that country and the factors leading to its reduction is given by Professor Niels Dungal in the *American Journal of the Medical Sciences*, 1956, Volume 212, and again in the *Archivos internacionales de la hydatidosis*, 1951, Volume 12.

Yours, etc.,

T. CLIVE BACKHOUSE.

School of Public Health and Tropical Medicine,
Sydney.
May 30, 1960.

MEDICAL RESEARCH IN AUSTRALIA.

SIR: It would be a pity if the recent interest expressed in the correspondence columns of this Journal in medical research be allowed to lapse.

I heartily concur with the sentiments expressed by others, that research should be placed on a firm footing in this young and active country. It should be obvious that the control or supervision of overburdened academicians is unnecessary. There is an erroneous impression that a young enthusiast on a humble grant can also produce research of a high standard.

Medical research does not necessarily depend on a chromium-plated centre with everything in it that opens and shuts; rather does it survive on the original thinking of the worker. There is a sad lack of true interest or application of ideas in this field on the part of clinicians.

At the moment, various bodies or funds have attempted to centralize donations and then to decide the allocation of same. I would query the overall ability or interest of anyone of the bureaucratic boards that run the various foundations in their ability to actively assess every one project. I know of no field investigations by such bodies.

An answer must surely depend on the meeting of all active workers in medical research to formulate common aims of purpose. This central body could readily evaluate any projects. The elimination of bureaucratic "dead wood' must surely follow.

Yours, etc.,

BERNARD BLOCH.

149 Macquarie Street,
Sydney.
May 23, 1960.

Post-Graduate Work.

SCHOOL OF PUBLIC HEALTH AND TROPICAL MEDICINE AND POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Post-Graduate Course in Industrial Health.

THE School of Public Health and Tropical Medicine and the Post-Graduate Committee in Medicine in the University of Sydney announce that a full-time course in industrial health, comprising lectures and visits to industries, will be held at the School of Public Health and Tropical Medicine, Sydney, from August 29 to September 16, 1960. Any interested medical practitioner is invited to attend. No fees will be charged.

Applications for enrolment should be sent to the Director, School of Public Health and Tropical Medicine, University of Sydney, before August 15, 1960. Further particulars are obtainable from Dr. G. C. Smith at the School.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Conference at Hornsby.

THE Post-Graduate Committee in Medicine in the University of Sydney, in conjuction with the Kuring-gai Medical Association, will hold a post-graduate conference at the Hornsby and District Hospital on Saturday and Sunday, July 2 and 3, 1960. The programme is as follows:

Saturday, July 2: 2 p.m., registration; 2.15 p.m., "Varicose Veins", Dr. C. H. W. Lawes; 3.45 p.m., "Hæmorrhoids", Dr. C. H. W. Lawes.

Sunday, July 3: 9.30 a.m., "Backache", Dr. W. D. Sturrock; 11 a.m., "Some Psychiatric Problems in General Practice", Dr. John McGeorge.

The fee for attendance at the course is £2 2s., and those wishing to enrol are requested to make early application to Dr. P. E. Gunton, Honorary Secretary, Kuring-gai Medical Association, 2 Pembroke Street, Epping. Telephone: WM 3044.

SEMINARS AT THE ROYAL NORTH SHORE HOSPITAL OF SYDNEY.

THE following is the programme of seminars at the Royal North Shore Hospital of Sydney from July to November, 1960.

July 5: "Recent Advances in Cardiac Surgery", Dr. Frank Mills.

August 2: "Clinical Enzymology", Dr. F. J. Radcliff.

September 6: "The Vectorial Approach to Standard Electro-Cardiography", Dr. Z. S. Freeman.

October 4: "Renal Angiography", Dr. B. Williams.

November 1: "Arteriography", Dr. J. K. Kalokerinos.

The seminars will be held on the first Tuesday of each month at 5.15 p.m. in the Students' Common Room. On the remaining Tuesdays a clinical demonstration will be held in the B2 Tutorial Room.

POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF ADELAIDE.

Course in New Scientific Techniques and Developments in Medicine.

THE following programme of lectures has been arranged for the second term of the Adelaide University year. The lectures will be held at 5.15 p.m. in the Verco Theatre in the grounds of the Royal Adelaide Hospital.

June 20: "The Application of Statistical Methods to Problems in Clinical Medicine: I", Dr. G. M. E. Mayo, Senior Lecturer in Genetics, University of Adelaide.

June 27: "New Techniques in Diagnostic Radiology", Dr. M. D. Begley, Tutor in Radiology, University of Adelaide.

July 4: "Statistical Methods in Medicine: II", Dr. G. M. E. Mayo.

July 11: "Electronics in Medicine", Professor E. C. Willoughby, Professor of Electrical Engineering, University of Adelaide.

July 18: "Statistical Methods in Medicine: III", Dr. G. M. E. Mayo.

July 25: "Radio-isotopes I: Structure of the Atom; Radiations and their Measurement", Dr. B. O. West, Senior Lecturer in Physical and Inorganic Chemistry, University of Adelaide.

August 1: "Statistical Methods in Medicine: IV", Dr. G. M. E. Mayo.

August 8: "Statistical Methods in Medicine: V", Dr. G. M. E. Mayo.

AUSTRALIAN VICE-CHANCELLORS' COMMITTEE.

Nuffield Dominions Trust: Appointments at Oxford Medical School.

The Registrar of the University of Oxford has advised that nominations are now invited from Australian universities to fill two appointments in the Oxford Medical School in the academic year beginning next October. The appointments are two demonstratorships tenable in any one of the following departments: biochemistry (three-year tenure preferred), human anatomy (two-year tenure preferred), physiology (two-year tenure preferred with possible extension to three). The appointments will be tenable for either two or three years, whichever is more convenient to the nominating university. Applicants are requested to indicate clearly the period of appointment agreeable to their university.

Medical deans have been supplied with information on the main research topics current in these departments. Duties will commence on October 1, 1960, or as soon thereafter as possible.

Conditions.

1. The qualifications for appointment to a demonstratorship shall be graduation at one of the Dominion universities and previous experience in research.

2. No person shall be appointed to a such demonstratorship who does not intend that immediately after such appointment shall terminate he will return to the Dominion from which he was appointed for at least five years' work of a like nature as that carried out by him during his appointment.

Applications.

Further information of the details and conditions of appointment under the Nuffield Dominions Trust and also of the requirements for application, may be obtained from the registrar of each of the Australian universities. Applications close on July 1, 1960, with the Secretary, Australian Vice-Chancellors' Committee, c.o. University of Melbourne, Parkville, N.2, Victoria.

Naval, Military and Air Force.

APPOINTMENTS.

THE following appointments, changes etc. are published in the *Commonwealth of Australia Gazette*, No. 23, of March 31, 1960.

NAVAL FORCES OF THE COMMONWEALTH.

Permanent Naval Forces of the Commonwealth (Sea-Going Forces).

Appointments.—Frederick John Palmer is appointed Surgeon Lieutenant (for Short Service) (on probation), dated 10th December, 1959.

Confirmation in Rank.—Surgeon Lieutenant (for Short Service) (on probation) David Alexander Noble is confirmed in the rank of Surgeon Lieutenant (for Short Service), with seniority in rank of 5th January, 1959, dated 5th January, 1960.

Citizen Naval Forces of the Commonwealth.

Royal Australian Naval Reserve.

Robert Fyfe Zacharin is appointed Surgeon Lieutenant, dated 2nd November, 1959.

Promotions.—Surgeon Lieutenants John Battson McCouat and Ben MacMahon Wadham are promoted to the rank of Surgeon Lieutenant-Commander, dated 23rd November, 1959, and 4th December, 1959, respectively.

AUSTRALIAN MILITARY FORCES.

Australian Regular Army.

Royal Australian Army Medical Corps (Medical).

3/40146 Captain J. J. Robinson is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (Southern Command), 13th January, 1960.

To be Captain, 8th February, 1960, with a Short Service Commission for a period of fourteen months.—6/4010 Connear Young.

To be Captain, 4th January, 1960.—QX700208 Lieutenant R. N. Hurley.

Citizen Military Forces.

Northern Command.

Royal Australian Army Medical Corps (Medical).—The provisional ranks of the following officers are confirmed.—1/39234 Captain P. Nicoll and 1/59814 Captain (Temporary Major) B. E. Todd. 1/25222 Major B. Bruce-Smith is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (Northern Command), 21st January, 1960.

Eastern Command.

Royal Australian Army Medical Corps (Medical).—2/137503 Captain (provisionally) R. T. Finch relinquishes the provisional rank of Captain, 29th January, 1960, and is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (Eastern Command) and is granted the honorary rank of Captain, 30th January, 1960.

Central Command.

Royal Australian Army Medical Corps (Medical).—The provisional ranks of the following officers are confirmed:—Captains 4/32104 W. G. Tucker and 4/32112 R. Hecker.

Western Command.

Royal Australian Army Medical Corps (Medical).—The provisional ranks of the following officers are confirmed:—Captains 5/26529 M. Traub and 5/26583 P. W. Burvill. F5/1220 Captain (provisionally) E. J. Gunn relinquishes the provisional rank of Captain, 11th February, 1960, is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (Western Command) and is granted the honorary rank of Captain, 12th February, 1960.

Reserve Citizen Military Forces.

Royal Australian Army Medical Corps (Medical).

Northern Command.—To be Honorary Captain, 15th February, 1960—John Ferguson.

Southern Command.—Honorary Captain E. Lowenthal is retired, 29th February, 1960.

The following officers are placed upon the Retired List (Southern Command) with permission to retain their rank and wear the prescribed uniform, 29th February, 1960: Lieutenant-Colonel (Honorary Colonel) W. E. E. Langford, Lieutenant-Colonel R. B. Maynard, E.D., and Major E. E. Price.

ROYAL AUSTRALIAN AIR FORCE.

Permanent Air Force.

Medical Branch.

Wing Commander H. T. Hardy (036451) is appointed to be Honorary Physician to His Excellency the Governor-General, 12th January, 1960.

The appointment of Wing Commander D. A. S. Morgan, O.B.E. (04398), as Honorary Physician to His Excellency the Governor-General is terminated, 11th January, 1960.

Flying Officer A. W. Harrison (0315074) is transferred from the Reserve and is appointed to a temporary commission, 1st January, 1960, with the rank of Pilot Officer (Student).

The following Pilot Officers (Students) are promoted to the rank of Flight Lieutenant:—K. E. Collins (042457), 4th

December, 1959; L. G. Trappett (015935), 8th December, 1959; A. H. Murphy (0212647), 9th December, 1959; R. P. Quirk (0314324), 21st December, 1959.

The resignation of Flight Lieutenant R. W. Munson (0218089) is accepted, 2nd December, 1959.

Squadron Leader G. C. Nelson (018487) is granted special leave without pay from 23rd November, 1959, to 22nd November, 1960, inclusive.

Active Citizen Air Force.

Medical Branch.

No. 25 (City of Perth) Squadron.—Flight Lieutenant T. A. G. Torda (0211567) is transferred to the Reserve, 1st January, 1960.

Air Force Reserve.

Medical Branch.

The following former officers are appointed to a commission with the rank of Flight Lieutenant:—D. T. Burke (0218197), 2nd May, 1959; S. A. Ward (039983), 28th May, 1959.

Douglas Cameron Mackenzie (433603) is appointed to a commission, 22nd December, 1959, with the rank of Flight Lieutenant.

The following are provisionally appointed to a commission, 6th December, 1959, with the rank of Pilot Officer:—John Lawrence Morrison (0116745), James MacDonald Reid (015330), Ian Stuart Wilkey (015329), Philip Martin Coghlan (0116194).

Flight Lieutenant M. DeL. Faunce (268115) is promoted to the temporary rank of Squadron Leader, 5th November, 1959.

The provisional appointment of Pilot Officer A. S. Luketina (040501) is confirmed and he is promoted to the rank of Flight Lieutenant, 4th December, 1959.

The notification regarding the termination of appointment of Flight Lieutenant (Temporary Squadron Leader) R. W. Greville (257932) as approved in Executive Council Minute No. 44 of 1959 appearing in Gazette No. 81 dated 17th December, 1959, is withdrawn.

Royal Australasian College of Surgeons.

FINAL FELLOWSHIP EXAMINATION.

A MEETING of the Court of Examiners for the final examination for fellowship of the Royal Australasian College of Surgeons will be held in Melbourne, commencing on Friday, October 21, 1960. Candidates who desire to present themselves at this examination should apply, on the prescribed form, to the Censor-in-Chief for permission to do so, before September 8, 1960. The appropriate forms are available from the Examination Secretary, Royal Australasian College of Surgeons, Spring Street, Melbourne, C.1. Candidates who have already been approved by the Censor-in-Chief, but who have not yet presented themselves for the examination, may present for this examination, provided they notify the Examination Secretary of their intention to do so by September 8, 1960. It is stressed that entries will close on this day, and late entries cannot be accepted. The examination fee is £26 5s., plus exchange on cheques drawn on banks outside Melbourne, and must be paid to the Examination Secretary by September 8, 1960.

The examination will be conducted in general surgery and in the special branches of ophthalmology, laryngo-otology, orthopædics, gynæcology and operative obstetrics, urology, thoracic surgery, neurosurgery, plastic surgery and pædiatric surgery.

At its meeting held on June 20, 1958, the Council of the College decided that candidates who possessed the fellowship of a body with which this College has reciprocity of primary examinations shall be exempted from the written part of the examination, provided that there is no relaxation of apprenticeship prerequisites.

FACULTY OF ANÆSTHETISTS: FINAL FELLOWSHIP EXAMINATION.

A MEETING of the Court of Examiners for the final examination for fellowship of the Faculty of Anæsthetists of the Royal Australasian College of Surgeons will be held in Melbourne, commencing on Friday, October 21, 1960. Candidates who desire to present themselves at this examination should apply, on the prescribed form, to the Assessor for permission to do so, before September 8, 1960. The appropriate forms are available from the Examination Secretary of the Faculty, Royal Australasian College of Surgeons, Spring Street, Melbourne, C.1. Candidates who have already been approved by the Assessor, but who have not yet presented themselves for the examination, may present for this examination, provided that they notify the Examination Secretary of their intention to do so by September 8, 1960. It is stressed that entries close on this day and late entries cannot be accepted. The examination fee is £26 5s., plus exchange on cheques drawn on banks outside Melbourne. The examination fee must be paid to the Examination Secretary by September 8, 1960.

Subjects for the final examination are: (*a*) anæsthesia and analgesia, including pre-operative and post-operative care; (*b*) medicine and surgery; (*c*) the application of the basic sciences, including chemistry and physics, to the specialty of anæsthetics. The examination in each case is partly written, partly oral and partly clinical (including the examination of patients).

Candidates are advised that the primary examination for Fellowship of the Faculty of Anæsthetists, Royal College of Surgeons of England, is reciprocal with the primary examination for Fellowship of this Faculty.

Graduates of an approved medical school who have obtained, prior to December 31, 1957, the first part of the diploma in anæsthesia of an approved medical school or college, may, at the discretion of the Board, be allowed to present themselves for the final examination of the Faculty, provided they have fulfilled all other regulations.

Notes and News.

Election to the Australian Academy of Science.

The only medical scientist elected to the Australian Academy of Science this year was Dr. S. Fazekas de St. Groth, Reader in Virology at the John Curtin School of Medical Research, Australian National University. Dr. Fazekas, who graduated in medicine and science in the University of Budapest during the war, came to Australia in 1947 to work with Sir Macfarlane Burnet at the Walter and Eliza Hall Institute. Here he carried out important investigations on hæmagglutination by influenza viruses, on the kinetics of multiplication of influenza virus, and on the experimental immunology of influenza in the mouse. In 1952 he joined Professor Fenner in the newly established Department of Microbiology in the John Curtin School of Medical Research, and has continued with his work on influenza virus. In 1954 he showed that "incomplete" influenza virus could be produced by treating susceptible cells with periodate, and since then he has been concerned principally with various aspects of the immunology of influenza. This work is being carried out at both the theoretical and the experimental levels, and promises to yield results of great importance in the understanding of virus neutralization and in practical aspects of vaccination against virus diseases.

Pharmaceutical Benefits Scheme.

All amendments to the schedules under the Commonwealth Pharmaceutical Benefits Scheme adopted since March 1, 1960, have been incorporated in a complete reprinting of the booklets issued under the scheme to doctors and chemists. The amendments operate from June 1, 1960.

The Commonwealth Department of Health proposes to incorporate future amendments to the schedules in the loose-leaf booklets by reprinting the entire page when a major change becomes necessary. This will avoid the need for doctors and chemists to amend the instructions by noting them in the booklets. Only in the case of a minor change that can be simply noted will the page not be reprinted.

The "Notes" to doctors and chemists issued with the schedules in the reprinted booklets are in a new form. Commenting on this change in the form of the "Notes", the Minister for Health, Dr. Cameron, said recently that an attempt had been made with the new "Notes" to present them in a form which was shorter, more convenient and more simply expressed. They had also been rearranged

under what it was felt would be more convenient headings. For the benefit of doctors and chemists already familiar with the operations of the scheme, however, it was stressed that the detail itself was in no respect changed. They were, in short, the old "Notes" in a new format.

Dr. Cameron said that the Pharmaceutical Benefits Advisory Committee was now examining a list of additional drugs for inclusion in the list of benefits. The committee in the course of its deliberations had sought the opinion of specialist sections of the medical profession concerning certain drugs. When those views had been received and considered, the committee would submit its final recommendations to him. Every effort would then be made to have the recommendations implemented as rapidly as possible. The machinery involved was considerable, but it was hoped to have the new drugs incorporated in the next issue of the booklets, which should be available on September 1, 1960.

Society for Medical and Biological Electronics.

The Society for Medical and Biological Electronics proposes to repeat in 1961 the course on "An Introduction to Electronics" currently being held in the Mining School Theatre, University of Melbourne. The present course comprises fifteen lectures and seven practical sessions, the three main topics being as follows: (i) "Circuit Elements"; (ii) "Basic Circuits"; (iii) "Electronic Instruments". Inquiries relating to this course should be directed to the Honorary Secretary of the Society, Mr. L. Bratspies, Mental Hospital, Mont Park. As enrolments in the course will be limited in number, it is suggested that the Society would be helped in planning the course by early inquiry from those interested.

The Charité, Berlin: 250th Anniversary.

The 250th anniversary of the *Charité* will be celebrated in Berlin from November 6 to 19, 1960, in connexion with the 150th anniversary of the Humboldt University. Applications for participation should be directed to the Committee for the Preparation of the 250th Anniversary of the *Charité*, Berlin N 4, Schumannstrasse 20-21, c.o. Dozent Dr. med. habil. Dagobert Müller, Secretary of the Committee.

An Honour for Professor R. E. J. ten Seldam.

Professor R. E. J. ten Seldam, Professor of Pathology at the Medical School of the University of Western Australia, has received an honour in the birthday list of Her Majesty Queen Juliana of the Netherlands. He has been appointed an Officer in the Order of Orange-Nassau.

Lip-Reading Classes for the Part-Hearing.

The Australian Association for Better Hearing (New South Wales Branch) wishes to draw attention to its lip-reading classes for people beginning to lose their hearing. The Association has always sponsored the teaching of lip-reading, which is now on the curriculum of the Education Department's evening college classes. Class fees and the cost of membership of the social club for the part-hearing are small, and the benefit gained in friendship and understanding is considerable. The Association's classes are conducted by trained teachers, and are held on Tuesdays and Fridays at 6.30 p.m. and on Wednesdays at 11.15 a.m. and 1.15 p.m. at the Australian Association for Better Hearing, 3 Bond Street, Sydney. Further information may be obtained on application to the Association.

University Intelligence.

UNIVERSITY OF WESTERN AUSTRALIA.

J. D. MARTIN, M.D. (London), M.R.C.O.G., has been appointed Senior Assistant to the Professor of Obstetrics and Gynæcology. Dr. Martin graduated from St. Thomas's Hospital Medical School, where from 1956 to 1959 he was Senior Lecturer in Obstetrics and Gynæcology. At present he is First Assistant in the Obstetric Unit at University College Hospital, London.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED MAY 7, 1960.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	1	2(2)	..	..	..	1	..	..	4
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	..	..	2	..	..	..	4	..	6
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	..	..	..	..	..
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	3	8(8)	1(1)	..	..	..	3	..	15
Diphtheria	1(1)	..	..	..	..	1(1)	..	..	2
Dysentery (Bacillary)	..	2(2)	..	..	2(2)	..	..	1	5
Encephalitis	..	2(1)	..	..	..	..	..	..	2
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	64(25)	26(19)	10(2)	13(6)	3(3)	..	..	1	117
Lead Poisoning	..	..	3	..	..	..	..	..	3
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	2	..	..	..	..	..	2
Malaria	..	..	1(1)	..	..	..	..	..	1
Meningococcal Infection	..	4(3)	..	..	1	..	..	..	5
Ophthalmia	..	..	..	..	1	..	..	..	1
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	..	..	..	..	2	..	..	..	2
Puerperal Fever	..	..	..	..	1	..	..	..	1
Rubella	..	5(5)	..	4(1)	..	..	..	..	9
Salmonella Infection	..	..	..	1(1)	2(2)	..	..	..	3
Scarlet Fever	15(6)	19(15)	1	1(1)	..	1	..	..	37
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	..	..	..	..	..	..	..
Trachoma	..	..	..	2(1)	2(1)	..	10	..	14
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	35(23)	17(15)	3(1)	4(1)	3(1)	3(1)	1	..	66
Typhoid Fever	..	1(1)	..	..	..	..	..	..	1
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

Dr. R. Paton, formerly Junior Assistant in the Department of Surgery, has been appointed Senior Assistant in Surgery.

Dr. J. H. Little, Senior Lecturer in Pathology, has been appointed Pathologist of the South Brisbane Hospital, Queensland.

At its meeting on November 16, 1959, the Senate conferred on 13 candidates *in absentia* the degrees of bachelor of medicine and bachelor of surgery. This was the first occasion on which these degrees had been conferred in the University of Western Australia.

In December, 1959, the Registrar of the General Medical Council, London, sent word that his Executive Committee had passed the following resolution:

> That the degrees of M.B., B.S. granted by the University of Western Australia be recognized for the time being by the Council under section 20 of the Medical Act, 1956, for the purposes of section 18 of the Act, as furnishing a sufficient guarantee of the possession of the requisite knowledge and skill for the efficient practice of Medicine, Surgery and Midwifery.

Australian Medical Board Proceedings.

NEW SOUTH WALES.

THE following additions and amendments have been made to the Register of Medical Practitioners for New South Wales, in accordance with the provisions of the *Medical Practitioners Act*, 1938 to 1958.

Registered medical practitioners who have complied with the requirements of Section 17 (3) and are registered under Section 17 (1) (a) of the Act: Dignan, Peter St. John Frederick, M.B., Ch.B., 1957 (Univ. New Zealand); Milencewicz, Witalius, M.B., B.S., 1959 (Univ. Adelaide).

Registered medical practitioners who have complied with the requirements of Section 17 (3) and are registered under Section 17 (1) (b) of the Act: Cole, Richard Barrett, B.Chir., 1957 (Univ. Cambridge), M.B., 1958 (Univ. Cambridge), M.R.C.P. (London), 1959; Debono, Francis, M.D., 1949 (Univ. Malta); Eppel, Isadore A'vigdor, M.B., B.Ch., 1952 (Univ. Dublin); Hunter, Lydia Jane, M.B., Ch.B., 1953 (Univ. Aberdeen), D.A., R.C.P. & S., 1956; Leitch, John Gibson, M.B., Ch.B., 1949 (Univ. Glasgow), F.R.C.S. (Edinburgh), 1959; O Sullivan, Diarmuid Pearse, M.B., B.Ch., 1942 (N. Univ. Ireland); Segal, Max, M.B., B.Ch., 1937 (Univ. Witwatersrand); Scott, Michael Burbridge, M.R.C.S. (England), L.R.C.P. (London), 1951; Weyland, George, M.B., B.S., 1954 (Univ. London), M.R.C.S. (England), L.R.C.P. (London), 1954; Wilbush, Joel, M.B., Ch.B., 1943 (Univ. Sheffield), M.R.C.O.G., 1950.

The undermentioned have been issued with licences under Section 21C (4) of the Act: Bokar, Peter Paul, from April 4, 1960; Nagy, Laszlo, Eastern Suburbs Hospital, from April 22, 1960; Sassi, Armando, Fairfield District Hospital, from April 22, 1960.

Medical Appointments.

THE undermentioned appointments have been made at the Royal Adelaide Hospital, Adelaide.

Dr. T. H. Beare has been appointed Honorary Visiting Pædiatric Physician (Northfield Wards).

Dr. G. G. Wyllie has been appointed Honorary Visiting Pædiatric Surgeon (Northfield Wards).

Dr. M. W. Brown has been appointed Honorary Clinical Assistant to the Ear, Nose and Throat Department.

Nominations and Elections.

THE following have applied for election as members of the New South Wales Branch of the British Medical Association:

Roche, James Barry, M.B., B.S., 1956 (Univ. Sydney), 21 Alison Road, Kensington, N.S.W.

Gould, Graham Roger, M.B., B.S., 1957 (Univ. Sydney), 168 Bondi Road, Bondi, N.S.W.

Lyons, Edward David, M.B., B.Ch., 1950 (Univ. Witwatersrand), c.o. Commonwealth Health Department, 39 York Street, Sydney.

Diary for the Month.

JUNE 13.—Victorian Branch, B.M.A.: Finance Subcommittee.
JUNE 14.—New South Wales Branch, B.M.A.: Executive and *Finance Committee.*
JUNE 15.—Western Australian Branch, B.M.A.: General Meeting.
JUNE 16.—Victorian Branch, B.M.A.: Executive of Branch Council.
JUNE 17.—New South Wales Branch, B.M.A.: Ethics Committee.
JUNE 21.—New South Wales Branch, B.M.A.: Medical Politics Committee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

ALL articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations, other than those normally used by the Journal, and not to underline either words or phrases.

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